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AMEBIASIS.

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Before discussing the subject of amebiasis I should like to present a brief statistical survey of the patients who were admitted to Charity Hospital in the year 1925. In this period of time 72 patients, from a total of over 25,000 admissions, were discharged with a diagnosis of amebic dysentery, but on reading over the histories of these patients carefully I was obliged to delete 21 of the cases for the reason that the data, at least as written down on the history, were not such as to complete a diagnosis. There is no doubt that the great majority of these patients had the disease, though the records are faulty.

Age. In the 51 definitely diagnosed cases the age incidence is of interest. Three patients were under the age of twenty years. Two of these were nineteen years and 1 was fifteen years of age. In the age period between twenty-one and thirty years there were 12 patients; thirty-one to forty years, 23 patients; forty-one to fifty years, 9 patients; fifty-one to sixty years, 2 patients; over sixty years there were also 2 patients—1 sixty-three years and the other sixty-five years of age. It is fair to assume from the patients who entered Charity Hospital that the greatest incidence of the disease occurs in the age periods of thirty-one to forty years; that the disease is extremely rare in patients under eighteen years and over sixty years of age, and a clinical curiosity in a child.

Sex. By far the largest number of patients were of the male sex, there being 46 males as contrasted with 5 females who suffered from amebiasis.

Color. The relative immunity of the colored race to the disease, amebiasis, is well exemplified by the incidence of the disease among the colored and white admissions to the hospital. Only 14 negroes suffered from amebic dysentery, whereas there were 37 of the white race. This is of moment because of the fact that negroes' hygienic habits, or lack of such, are decidedly more faulty than those of the white man, yet in spite of this, fewer colored men develop the disease than white, indicating a tendency to racial immunity.

Symptoms of the Onset. The chief complaint which brought the patient to the hospital in 40 of the cases was diarrhea. Thirteen patients came in because they suffered from rather severe abdominal cramps, which to them was of greater import than the accompanying diarrhea. A few of the patients came in because of a combination of these two symptoms. Only 1 patient came in because of gradually increasing weakness, whereas 7 were admitted because of loss of weight. Two were admitted on account of rectal pain and 1 because he thought he had bleeding hemorrhoids.

The Duration of the Disease. In this series of cases of amebic dysentery and diarrhea the duration of symptoms varies from two weeks to thirty years. Quite regularly it was found that the patients said they had had diarrhea for three years, four years, eight years, ten years, twelve years and even in 1 case for thirty years. On the other hand, in patients who had the more severe symptoms, which we will classify as dysentery, the duration was very much shorter—from a few weeks to a month.

Repetition of Attacks. One of the features of amebiasis is a tendency to repetition of diarrheal attacks. The repetition of attacks, the duration of these attacks and the interval between the attacks vary considerably. One patient had his first attack in 1910 and did not have a second attack until 1926. Another patient in fifteen years had had three attacks. Still another patient in twelve years had had an attack every year for four years. The remaining eight years he had a mild attack of diarrhea about once a month. Occasionally you get definite, specific information as to the number of attacks and their duration. One man in three years had ten periods in which he suffered for a week or two varying degrees of diarrhea. Another in a period of seven years had had fifteen seizures with diarrhea and cramps.

Social History. These patients necessarily came from the lower walks of life, as would be expected in a large charity hospital. They represent various occupations in life, none of which seem to have any direct bearing upon the disease. The majority of them apparently got the disease in this locality, Louisiana. In only 1 patient was there a history of having developed the disease while in the tropics.

Physical Examination. Tenderness and rigidity of the abdominal wall was seen in 21 cases. In 5 cases only was there sufficient distention to be noted and in only 5 cases was the liver found enlarged.

Proctoscopic Examination. Proctoscopic examination was done in every one of the 51 cases. The usual, typical picture of amebic proctitis was found—congestion of the mucous membrane, ulceration and the ulcers covered with mucus, which was bloody and which contained the ameba in large numbers. This is of interest, showing the direct association of dysentery and ulcerated rectum.

Treatment. A variety of treatment was carried out upon these patients. Yatren, as reported by Turner and Jones,[1] apparently has been most successful and was employed in 24 cases; stovarsol in 7 cases. Emetin and ipecac alone and in combination with stovarsol, was used in the other cases. Emetin in 3 cases was followed by a relapse.

Discussion. Let us now discuss amebiasis in general, with more particular attention to the disease as it manifests itself in specific individuals. A good working classification of amebiasis is given by Dobell and Low.[2] They divide the disease into four clinical groups: (1) Carrier; (2) general amebiasis; (3) amebic diarrhea; (4) amebic dysentery.

I shall exemplify three of these four groups by specific instances as the disease occurs in a particular individual. I will not give the history of a carrier, but will simply discuss in a general way the carrier state.

1. *Carrier.* In order to understand the carrier state it is necessary to know how the disease is transmitted and to know something of the life cycle of Endameba dysenteriæ. The endameba passes through two stages—encysted and vegetative. In the first stage, or cystic stage, we have the protozoa passing out of the rectum of a carrier, that is, some individual in whom the organisms have become encysted, and subsequently being ingested by some other human being, entering the intestinal tract of this individual. The cysts, after they enter the intestines of this next person, have their cyst wall digested off; possibly it is held by the action of the pancreatic ferments, though Johns (personal communication) says that fresh duodenal contents have no effect on the cyst wall and that the process of liberation of the encysted protozoa is probably through a process of autodigestion of the cyst wall under favorable circumstances. The ameba in this form, with its four nuclei, passes down to the large gut, where it sporulates and liberates small motile amebæ, which enter the mucous membrane of the large gut, developing into full-grown amebæ. Some of these latter newly formed amebæ may pass out of the intestinal tract. Others do not and become encysted in the lower portions of the colon when the feces become inspissated. If the tissue resistance of the host is able to overcome the invading amebæ, we have the minimal destruc-

tion of the tissues, and this is very slight in so-called carriers, probably with immediate repair. Consequently, these individuals suffer from practically no symptoms whatsoever, though occult blood is regularly found in their stools. This state of affairs is undoubtedly present in the great majority of cases in which its organisms enter the intestinal tract. The amebæ having attained the vegetative form, and being incapable of causing symptoms in a second person, divide or become encysted. When they pass from the mucous membrane of the large intestine to the lumen of the gut they encyst and then they develop their four nuclei from the mononuclear stage, become more or less desiccated and pass out again as cysts. These carriers more or less continuously passing cysts are almost without symptoms. They are necessary, however, to the propagation of the disease and the carriers outnumber by far the individuals who have symptoms of diarrhea or dysentery. Various statistics have been presented as to the incidence of carriers in relation to those who suffer from the symptoms of amebiasis. The carriers are supposed to represent as high as 95 per cent of the individuals infested with amebæ. These figures are probably too high. They are based very largely on investigations that were made on the stools of men in the army, young and healthy individuals presumably. A general cross-section of the whole public would probably show that the carriers do not form quite such a large percentage of those infested with amebæ. That the carrier stage is easy to develop, but that the stage of symptoms is infrequent, is shown by some experiments made in the Philippines, where 18 men volunteered to ingest amebic cysts. Only 3 of these men developed any symptoms and of these 3, 1 had to be infected five times before he developed any manifestations of the disease. In the other 15 men the organisms entered the intestinal tract and there underwent their life cycle and these men became carriers. They were, of course, subsequently cured. Of the 3 men who developed symptoms, 1 man developed symptoms a week after the ingestion of the cysts, 1 twenty-eight days and the other fifty-six days later—figures which show that there is no such thing as an incubation period in its relation to amebiasis.

The virulence of any particular strain of ameba seems to be of no importance. Symptoms depend upon the resistance of the host rather than upon the virulence of the organism. Inject a virulent bacterial strain in a group of men and the majority would develop symptoms. The contrary holds true of amebæ. The majority of the population is resistant to these protozoa and a considerable section of the population has to be infected in order to get a relatively few cases of the disease. Animals are hard to infest with amebæ. Practically the only animal that can be readily infested is a kitten, a fact of some importance as a differential test of the types of ameba, because injecting into the rectum of kittens material con-

taining Endameba dysenteriæ results in the kittens developing dysentery. As soon as the kitten becomes a cat it is hard to infest. Sellards and Baetjer, in some work done at Johns Hopkins a few years ago, with difficulty were able to bring about reproduction of amebæ in the colon of a guinea pig.

The endameba is pathogenic to man only, and is the only ameba which is pathogenic to man. Endameba coli is nonpathogenic, and these amebæ live as a harmless parasite in the host. Endameba dysenteriæ is an obligatory parasite and in order to carry out its life cycle it has to live off the tissues and juices of man.

2. *General Amebiasis.* If the carrier has more pronounced symptoms he moves into the second class and is considered to have general amebiasis. The history of a patient with chronic arthritis will illustrate this stage of the disease. This man has had from time to time slight attacks of diarrhea which were very slight indeed and which he has had for eighteen years. Six years after the first attack his joint condition began. In addition, at no time was he entirely free from intestinal symptoms. He has a certain amount of so-called intestinal indigestion, occasionally with a slight amount of discomfort. A history such as this is quite typical. These individuals have an ease of fatigability, a general lack of tone and an absence of a feeling of well-being which the normal individual should have. Diarrhea is usually of minor importance, but there are symptoms referable to the gastrointestinal tract. There will be a loss of appetite, sometimes slight gastric disturbance and more pronounced intestinal discomfort, the changes which we are wont to speak of as fermentative in type. The average normal individual is not aware of the organs of his body. The normal man knows when he is hungry and that is practically his only realization he has that he has a stomach. He is conscious of his intestines only when he has a desire to defecate. Patients with general amebiasis, on the contrary, are intestine conscious. Other symptoms, general in character, are present. They are more or less anemic and sometimes under weight. Often careful questioning will develop still more symptoms, such as vague pains in the arms or legs. As with the present patient, an arthritis is occasionally present. In this particular individual the arthritis is not associated with pain, but he has a definite fixation of the terminal pharyngeal joints. He has discomfort but not true pain in the other small joints and some of the larger joints. Arthritis as a complication of amebiasis is an interesting subject of discussion. Kofoid and his coworkers on the Pacific Coast have gone so far as to suggest that most cases of arthritis are due to amebiasis. On the other hand, as pointed out by Johns, it would seem more likely that bacteria or bacterial toxins enter the general circulation than amebæ from the chronic ulceration to produce the chronic deforming arthritis. Incidentally, it is well to get a detailed history of a man who has an arthritis

when one is attempting to elucidate the etiologic problem of that particular case.

3. *Amebic Diarrhea.* If an individual suffering from general amebiasis develops well-marked intestinal symptoms, then they will develop the next clinical type of this disease, namely, amebic diarrhea. As a carrier at any time is prone to develop symptoms of general amebiasis, so the individual with general amebiasis may develop the symptoms of amebic diarrhea. The man with amebiasis will often give a history of diarrhea of mild type of forty-eight to seventy-two hours' duration. When we have the more pronounced symptoms of amebic diarrhea we will get a history such as is given by a young man, aged twenty-nine years, whose disease began three weeks ago as a watery diarrhea with mucus and blood in the stools and about eight movements a day. This young man has some slight pain during his movements. Apparently he has no disturbance in his digestion and has no complaint at all except the diarrhea of three weeks' duration. He has lost some 7 pounds in weight. Practically the only discomfort that he has arises from the necessity of having an evacuation as frequently as he does. He is well nourished, well developed and, except for the proctoscopic examination, his physical examination discloses nothing. He has a slight anemia. This type of diarrhea, slight in character, is of interest because it is in this type of individual that an hepatic abscess is likely to develop. It is not the man who has general amebiasis and amebic dysentery, but it is the man with the slight diarrhea who develops this relatively frequent complication of amebic infestation of the intestinal tract. Indeed, it is quite possible that the diarrhea may be so slight as to be overlooked, yet the patient have an amebic abscess. Incidentally, an abscess often develops quickly after the first symptoms of diarrhea. In the production of hepatic abscess the parasites are carried from the intestinal tract by way of the portal system into the liver. There they produce usually a general hepatitis, occasionally going on to multiple abscess formation but very much more frequently to a single abscess. The single abscess is observed in a large percentage of cases in the right lobe of the liver, and it has a tendency to point upward toward the diaphragm, rupturing under the diaphragm or through the diaphragm.

The first case of liver abscess that I saw in New Orleans taught me, besides the possibility of a patient having an abscess without a history of diarrhea, several other things of importance, one of which was not only to examine the front of the abdomen, but also to make an examination of the individual's back. This first case occurred in a man who had no knowledge of ever having had amebic dysentery and whose stools had been repeatedly examined. He had had influenza in the fall and developed signs at the right base of his chest, which persisted. For a period of several months he

was unable to work on account of a slight temperature rise associated with weakness and exhaustion. Because of his previous history of influenza or bronchopneumonia and because of the persistent fever and of the physical signs at his right base, it was believed that he had an empyema. For some weeks, because of these distant breath sounds and impairment in the percussion note it was believed that he had pleural pus and the chest wall was repeatedly punctured without effect. Finally, the thought occurred that he might have a liver abscess pressing up on the diaphragm and, as a result of the extension of inflammation, producing the signs in the pleura. An exploratory operation was performed and a fairly large liver abscess was found. This was evacuated and the patient made an uneventful recovery and he is now up, well and strong.

4. *Amebic Dysentery.* The classical textbook picture of the disease, amebic dysentery, is exemplified in the history of most of the patients who have been admitted to the hospital in the past year. These patients really represent a very small percentage of those who are infected with Endameba dysenteriæ, probably not more than 0.5 per cent. Incidentally, hepatic abscess is found more rarely. It is estimated that 1 out of 20 who have amebic diarrhea or dysentery develops an abscess. Classical symptoms of amebic dysentery are so typical that a presumptive diagnosis may be made simply from the recital of a man's story. Frequent stools associated with marked tenesmus, cramplike pain and an ineffectual desire to defecate at very frequent intervals is the common history. The stools contain very little fecal matter, probably nothing but blood and mucus and amebæ in enormous numbers. The patient wastes very quickly. A well-known English authority on amebic dysentery says that there is only one other condition with which he is acquainted in which such rapid wasting occurs and that is obstruction of the esophagus. These patients go down hill very quickly and sometimes will die within ten days or two weeks of the onset of their symptoms. The first case of amebic dysentery that I ever saw was a case of real dysentery. Because of the supposed rarity of the disease in the North, it had not been recognized until by the astuteness of Dr. Warfield Longcope the possibility of this disease was suggested to the surgeon in attendance. Not until a stool examination was made was the condition recognized. This young man complained of extremely severe diarrhea which had been preceded for some weeks by pain in the liver region. Because of the pain and enlargement of the liver he had been treated for syphilitic hepatitis, although he denied absolutely that he had had syphilis. After Dr. Longcope had discovered the amebæ in the stools and the patient was put upon emetin, his symptoms rapidly improved, although I believe that at a later period it was necessary to drain a liver abscess.

From the epidemiologic standpoint a patient with acute amebic

dysentery is of little interest. He is of no danger to his fellow man. He passes only active, vegetative forms which will do no harm, as amebæ cannot complete their life history without becoming encysted first. If amebic dysentery and amebic abscess were the only two types of amebiasis, amebic disease would disappear from the earth. The cysts have to go from one host to another and they have to enter an individual as a cyst. They get into that individual not only by direct contact but also by his drinking water or taking material which has been treated with polluted water. Water transportation of amebæ is of some importance. Cysts are destroyed rapidly by desiccation. Moisture and a certain amount of heat (though heat is not as important as moisture) are necessary for the viability of the organism. The cysts will live for many days in suitable media, such as semisolid, moist stools. Transmission by flies is supposed to be rare, but viable amebæ have been found on the fly and in its intestinal tract. Inference would point to the fly as a more common vector than he is generally thought to be.

What I have said about the diagnosis of amebic dysentery from the history alone is true. Confirmatory evidence should always be obtained by proctoscopic examination and by examination of the bloody mucus on the mucosa of the lower gut. The presence of ulcerative lesions covered with blood and mucus seen on the rectal mucosa through the proctoscope just about clinches the diagnosis—the absolute proof, of course, is the finding of the amebæ, which should be looked for immediately in material taken directly from an ulcer, if possible, as the organisms have a tendency to burrow into the mucosa. The presence of motile organisms containing ingested red cells in material removed from a lesion is absolutely pathognomonic of the pathogenic variety of the parasites. They are easy to recognize as Endameba dysenteriæ. The presence of red blood cells in these motile organisms serves to differentiate them from other types of endameba. One word of caution: the diagnosis of cysts of Endameba dysenteriæ is very difficult. It takes a competent protozoölogist who has made an intensive study of the different types of ameba to make such a diagnosis. The same thing applies to the precystic ameba.

Summary. A review of the cases of amebiasis occurring in the Charity Hospital in the past year is presented. A working classification is discussed, together with the clinical manifestations of several classes. It is believed that the disease, amebiasis, occurs much more frequently than is generally considered to be the case. Amebiasis is undoubtedly common in the far South and in some of its manifestations, at least, is more frequent in the North than is generally recognized.

REFERENCES.

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2. Dobell and Low (quoted from Byam and Archibald): Practice of Medicine in the Tropics, 1922, **2**, 1343.

CERTAIN CLINICAL AND PATHOLOGIC ASPECTS OF LYMPHOSARCOMA.

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Kundrat,[1] who first described the disease now familiarly known as lymphosarcomatosis, defined the unit of growth as a malignant tumor of lymph nodes or of other lymphoid structures in which lymphocytes proliferate diffusely in an inconspicuous stroma of connective tissue. He predicated a tendency on the part of the growth to confine itself within more or less sharply defined geographic limits, but noted its proclivity to expand locally and often ruthlessly. The present paper is a record of 17 cases of lymphosarcoma encountered among 11,925 autopsies at Bellevue Hospital. Of the 17 cases, 9 illustrated rather faithfully Kundrat's maxim of local growth; the remaining 8, however, displayed little, if any, inclination to spare tissues, regionally or otherwise, but brought about a degree of territorial expansion seldom distanced by any of the other diseases of the lymphoid apparatus.

There are several conditions which are characterized by histologic changes in the lymph nodes and elsewhere similar to, or identical with, those of lymphosarcoma or by related naked-eye alterations in the same locations, namely, chronic lymphatic leukemia, Cohnheim's pseudoleukemia, Hodgkin's granuloma, certain varieties of tuberculosis of the lymph nodes, and the disease recently described under the title of follicular lymphadenopathy with splenomegaly.[2] Clinically, lymphatic leukemia may be excluded by the changes in the blood, while anatomically the distribution of its lesions differs from that of lymphosarcoma in that lymphatic leukemia is practically always attended by splenomegaly and by generalized enlargement of the lymph nodes, whereas in lymphosarcoma, the spleen is not commonly enlarged, except in fortuitous circumstances, and the lymphoid hyperplasias tend oftener to confine themselves to a restricted region. Histologically, the changes in the lymph nodes in the two diseases may be strikingly alike, although here, again, it is sometimes possible to exclude leukemia by the presence in the vascular channels of increased numbers of lymphocytes. Pseudoleukemia, on the other hand, presents no blood changes to distinguish it from lymphosarcoma, and between them histologic differences in the lymph nodes and elsewhere are not discernible. However, pseudoleukemia produces no destructive infiltration of tissues, but limits its activities to the lymphoid structures, and the spleen is almost invariably enlarged, whereas the opposite is not unusual in

lymphosarcoma. Clinically, lymphosarcoma is most often mistaken for Hodgkin's disease, since in both of them the visible and palpable lymph node enlargements not infrequently present certain features in common. Moreover, there are those cases in which the arrangement of the deeper lesions, lymph node and visceral, is such that the two may be confounded, although, in the majority of cases, the lymph node enlargements in Hodgkin's disease are of wider extent than in lymphosarcoma, where, as mentioned, they sometimes tend to remain regional. In most cases of Hodgkin's disease, the spleen is enlarged and presents greater or less numbers of whitish nodules composed of the same sort of tissue as that in the lymph nodes, while in lymphosarcoma the spleen, if it enlarges at all, often does so as the result of some independent process. The several and intimate resemblances between lymphosarcoma and Hodgkin's disease will be referred to throughout this paper and, wherever dissimilarities arise, they, too, will be noted. This has a practical as well as an academic interest for the physician, who, it seems to me, is rarely justified in arriving at a clinical diagnosis of Hodgkin's disease without a mental reservation to the effect that the condition might really represent lymphosarcoma, so closely may they resemble one another. Usually the two may be separated once and for all by excision and microscopic examination of an involved lymph node, since the histology of Hodgkin's disease is distinctive and different from that of lymphosarcoma. Also, it is to be mentioned that the clinical distinction between lymphosarcoma, particularly of the thoracic and cervical nodes, and certain forms of lymph node tuberculosis is not often to be lightly achieved, although here, again, examination of an excised node is the best single aid to such an accomplishment. That the lymph nodes in Hodgkin's disease and lymphosarcoma are discrete, and hence movable against themselves and against the overlying and deeper structures, and that the reverse is apt to obtain in tuberculous lymphadenopathy, is a valuable, if overvenerated, diagnostic criterion which, however, is sometimes rudely violated. Occasionally the lymph nodes in Hodgkin's disease are fused, and in 1 case I have observed ulceration of the overlying integument. The present paper refers to 2 instances of fixation of the lymph nodes in lymphosarcoma, 1 with ulceration of the skin. Conversely, on 5 occasions I have seen extensive tuberculous lymphadenopathy with discrete and unattached nodes. Finally, in the so-called follicular lymphadenopathy, there is moderate but generalized enlargement of the superficial lymph nodes with splenomegaly, the clinical picture thus providing a perfect counterpart of Hodgkin's disease and of certain cases of lymphosarcoma. In follicular lymphadenopathy, however, excision and microscopic examination of an enlarged node reveals characteristic changes in the form of an extraordinary degree of hyperplasia of the germinal follicles, so

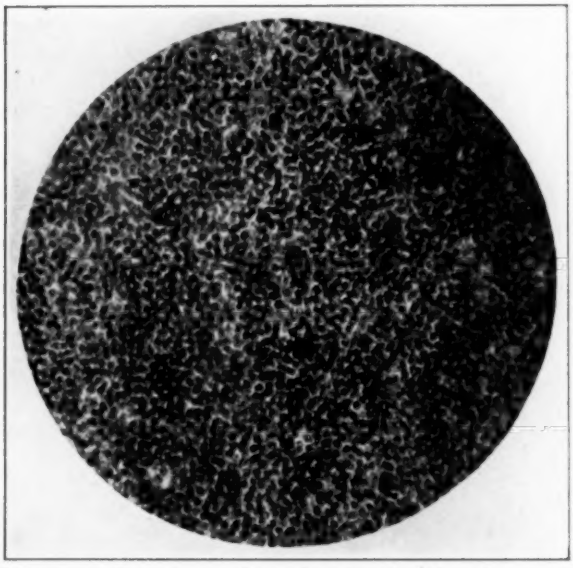

FIG. 1.—High-power photomicrograph of a lymph node in lymphosarcoma, showing simple diffuse hyperplasia of lymphoid cells.

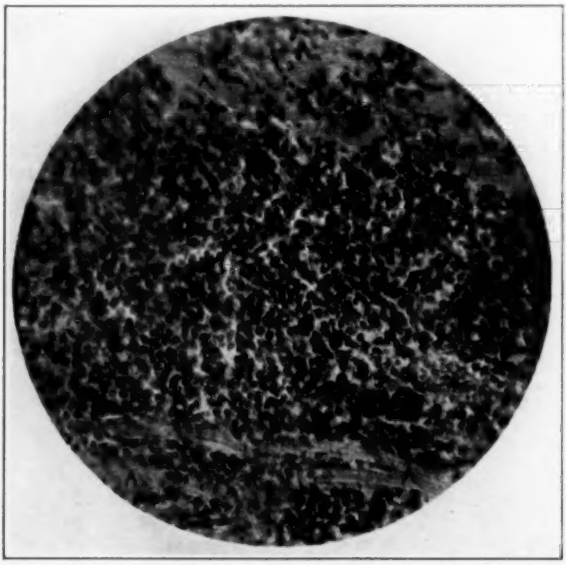

FIG. 2.—High-power photomicrograph showing horde-like infiltration of lymphocytes between the heart muscle fibers, the remains of which are to be seen at A. From a thymic lymphocarcoma. (Case II.)

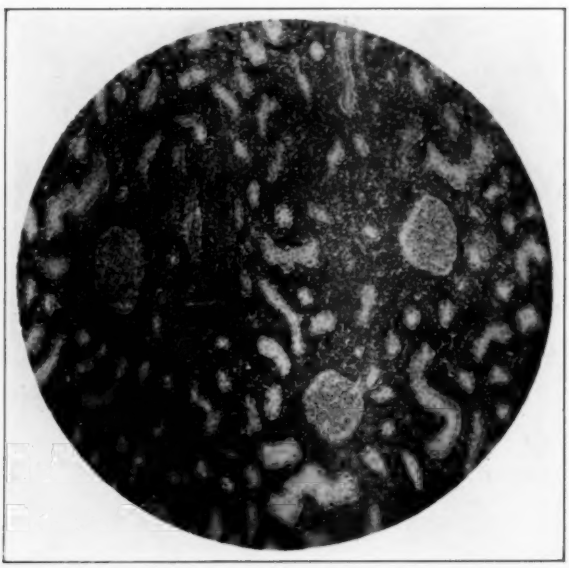

FIG. 3.—Low-power photomicrograph showing widespread lymphocytic infiltration of the interstitial structures of the kidney. From a case of lymphosarcoma of the thymic remains in which the kidneys were massively enlarged because of dense infiltration of lymphocytes from cortex to pelvis, the kidneys, together, weighing 1300 gm. (Case II.)

that its histologic differentiation from lymphosarcoma and Hodgkin's disease may be completed at a glance.

Even from this cursory review, it is obvious that the clinical separation of the members of this group of diseases is beset with difficulties and that, without accurate blood counts and particularly without the aid of biopsy, these difficulties are impossible to surmount. After all ascertainable facts have been considered, however, and when each of these lesions is segregated according to its lights, lymphosarcoma remains as an entity sufficiently endowed with peculiarities of its own to establish its claim to individuality.

In assembling these cases for presentation, I have divided them into groups according to the predominance of the lesions and have attempted to accent the clinical import of their anatomic revelations, since accurate differentiation in the living subject is essential from the standpoint of prognosis. In this manner, one series of 5 cases is presented that is characterized by predominant enlargement of the lymph nodes; a group of 4 cases by predominant involvement of the lymphoid structures of the gastrointestinal tract; one of the prostate gland, and a series of 7 cases of lymphosarcoma of the thymic remnants marked by ravenous destruction of neighboring tissues, in 2 of which death occurred after the intervention of acute leukemia.

Case Reports. Lymphosarcoma of the Thymic Remains. CASE I.—M. C., a baker, aged twenty-five years, was admitted to Bellevue Hospital on April 9, 1914. It was impossible to obtain a satisfactory history, but it was learned of him that, two and a half months before admission, a tumor-like mass appeared below the angle of the left jaw and a month later a similar mass became noticeable on the opposite side. Both gradually increased in size and the patient began to complain of difficulty in breathing that steadily increased.

At the time of admission to the hospital, he presented marked orthopnea and cyanosis of the face. Large, freely movable masses were present on both sides of the neck and the axillary and inguinal lymph nodes were enlarged. The feet and legs were edematous. Percussion of the chest showed diminished resonance along the inner border of the right scapula. On the left side, breath and voice sounds were diminished and expansion was limited. Over the right lung respiration was noisy and harsh, and there were bronchial râles, together with a to-and-fro friction rub along the right border of the sternum. Palpation of the abdomen revealed a large mass in the left upper quadrant.

Autopsy. The mediastinum, corresponding to the position normally occupied by the thymus, was completely filled by a huge tumor which, on section, presented a pale, glistening, homogeneous appearance. The mass insinuated itself around the great vessels at the base of the heart and posteriorly to include the esophagus, trachea and bronchi. The upper portion of the esophagus was compressed and irregularly infiltrated by tumor tissue. The left primary bronchus was similarly infiltrated and almost completely occluded. Likewise, the walls of the superior vena cava were invaded. The growth penetrated the pericardium and both auricles and infiltrated the epicardial fat over the right ventricle. The right tonsil was enlarged to the extent of about 3 cm. and, beneath the ramus of the

left jaw, there was a solitary lymph node likewise measuring about 3 cm. in length. Otherwise the cervical nodes were free, as were the inguinal, femoral, retroperitoneal and iliac nodes. The nodes around the pancreas, however, were enlarged to an enormous extent and the pancreas itself was diffusely infiltrated by whitish tumor tissue, identical in appearance with that described elsewhere. In the wall of the small intestine were several nodules which measured about 3 cm. in diameter, the tissue having the same appearance as that elsewhere described. In the lower pole of the right kidney was a nodule measuring 1½ cm. in diameter.

Histologically, sections from the growth in the thymic region and from the enlarged lymph nodes showed a rich aggregation of lymphocytes supported in a moderately cellular framework of connective tissue. Identical foci were found in the heart muscle, kidney, pancreas and the wall of the gut.

Case II.—The patient, a man aged twenty-six years, a butcher, was admitted to Bellevue Hospital, complaining of shortness of breath. He said that three weeks before admission he suddenly experienced difficulty in breathing and became subject to severe cough, attended by pain in the chest and expectoration.

Physical examination revealed, in addition to dyspnea, cyanosis of the finger tips, edema of the subcutaneous tissues, and ascites, together with slight bulging of and dullness over the lower right side of the chest, and dullness beneath the right infraclavicular region and between the scapulæ. The area of cardiac dullness was increased, but the apex beat was neither visible nor palpable and the heart sounds were muffled. The urine showed a trace of albumin and hyaline and granular casts. The blood revealed 13,000 leukocytes, of which 66 per cent were polynuclear neutrophils and 34 per cent lymphocytes.

Autopsy. On section, the subcutaneous tissues were universally edematous. The peritoneum was thickened, opaque, and enclosed several liters of yellowish fluid. On lifting the sternum, the anterior mediastinum was found to be occupied by a growth which measured 9 by 13 by 10 cm. and which conformed in a general way to the shape of the normal thymus. On section, the growth was made up of yellowish-white tissue, divided by fibrous bands into lobules of variable size. The tumor extended downward as far as the level of the auriculoventricular groove and upward to within a short distance of the lower border of the thyroid gland. Laterally it infringed on the root of the left lung and bands of tumor tissue extended along the connective tissue planes around the larger bronchi for a distance of several centimeters. The substernal, peribronchial, peritracheal and lower cervical nodes were enlarged, discrete, the largest approximating the size of a cherry. The pericardium contained about 200 cc. of turbid fluid with fibrin flocculi, and both layers were covered by fibrinous exudate. The heart was greatly increased in size and the epicardial fat was diffusely infiltrated by grayish-yellow tissue, similar to that of the growth in the region of the thymus. The walls of both ventricles were enormously thickened and rigid, and were largely replaced by grayish-yellow tumor tissue, only islands of reddish musculature showing through at intervals. The parietal and diaphragmatic pleuræ on the right side measured 0.5 cm. in thickness and were adherent to the chest wall, pericardium and diaphragm through the medium of infiltrating tumor tissue. The kidneys were massively enlarged and weighed, together, 1300 gm. Each measured 17 by 8½ by 8 cm. The cortices were unusually broad and grayish in color, standing out in contrast to the dark-red pyramids. On section, the cut surface was smooth, pale, the substance bulging and glazed.

Histologically, sections from the mass in the thymic region revealed a markedly cellular growth composed of lymphocytes, the cells in places

being closely packed, in other places grouped in islands of various sizes, in still other places presenting a streaklike alignment. In the lymph nodes the cellular unit was morphologically identical with that in the thymic growth, but the distribution of the cells was diffuse rather than insular or striate. In both the thymic and lymph node growths, the connective tissue was well vascularized. In the heart muscle, incursion of lymphocytes occurred to an amazing extent, almost every individual muscle fiber being separated from its fellow by a dense infiltrate of lymphocytes, the muscle fibers compressed and their transverse striations lost. Sections from the kidney disclosed interstitial invasion by lymphocytes in proportions no less prodigious than those encountered in the heart, the infiltration extending from pelvis to cortex, bringing about wide separation of the uriniferous tubules. Except for minute interstitial lymphomatous deposits in the liver, the remaining organs showed nothing worthy of note.

Case III.—H. L'H., a man, aged fifty-eight years, was admitted to Bellevue Hospital April 8, 1921. He stated that, in March 1918, he noticed a swelling in the right side of the neck that gradually increased in size. Radium treatment was instituted in September of that year and, in the course of the next two months, the swelling disappeared and the patient thought himself cured. In February, 1920, however, a similar swelling appeared on the left side of the neck. Radium treatment was commenced in the following March, and the swelling was reduced in size, but soon increased again. In December, 1920, the patient began to suffer from shortness of breath, followed by difficulty in swallowing and speaking.

At the time of admission to Bellevue Hospital, about four months later, physical examination revealed a large mass in the left side of the neck, together with enlargement of the inguinal nodes on both sides and of the axillary nodes on the left side. The left side of the chest bulged markedly and the skin over it was edematous, the corresponding superficial veins were engorged, and the left arm was edematous to such an extent as to interfere with motion. There was dullness over the upper half of the left lung anteriorly and posteriorly, and bronchial breathing throughout both lungs. The liver was palpable 3 cm. below the costal margin. The lower extremities were edematous. The blood count revealed 12,300 white cells, of which 90 per cent were polynuclear neutrophils, 9 per cent lymphocytes and 1 per cent transitionals.

Autopsy. Inspection of the body revealed immense swelling and edema of the left arm and hand. On both sides of the neck were huge masses of enlarged lymph nodes that were firmly attached to the skin and to the underlying structures. On the left side of the neck, behind and at about the middle of the sterno-cleido-mastoid muscle, the skin was eroded, giving rise to an irregularly rounded ulcer which measured 5 cm. in diameter, the edges sloping, the base reddish and granular. In the lower portion of the left axilla was a solitary mass which lay immediately beneath the skin, was somewhat egg shaped and measured 6 cm. in length and 3 cm. in diameter. It was firmly attached to the skin and was only slightly movable against the deeper structures. The inguinal lymph nodes on both sides were palpably enlarged. On opening the chest, each pleural cavity was found to be occupied by about 250 cc. of brownish fluid, while a huge tumor came into view in the region normally occupied by the thymus. The tumor was firm to the touch, cream colored and measured 17 by 10 cm. Its shape was comparable to that of the normal thymus body. The growth, extending downward, infiltrated the pericardium and completely replaced the muscular structures of the right auricle of the heart. In a backward direction, it molded itself around the structures at the base of the heart, including the aorta and pulmonary artery, and around the upper part of the esophagus. Direct extensions from the growth covered the parietal pleura above the

apices of the lungs, forming thick, cream colored, nodular sheetings. Near the bifurcation of the trachea, a large nodule projected directly into the esophagus in such manner as to lift the mucosa without, however, producing ulceration. At the bifurcation of the trachea, the larger bronchi were surrounded by tumor tissue. The right bronchus was markedly compressed and its mucosa superficially eroded, while in its walls, particularly posteriorly, were cream-colored islands of tumor tissue. The left bronchus, immediately below the bifurcation, presented five or six cream-colored bands of tumor tissue which ran circumferentially and replaced the cartilaginous rings for a distance of about 4 cm. The mass grew upward into the neck, where the soft tissues were directly and extensively infiltrated, the infiltration extending as far as the level of the lower jaw on both sides and as far backward as the trapezius muscle. Around the abdominal aorta, near its bifurcation, were a dozen or more enlarged lymph nodes, the largest measuring 4 cm. in length and 2 cm. in thickness. These, on section, presented much the same appearance as the tumor tissue described elsewhere. In the immediate vicinity of the head of the pancreas were several enlarged nodes, the largest measuring 5 by 3 cm. The spleen, which measured 15 by 8 cm., was free from all indications of tumor growth.

Histologically, the growth in the region of the thymus and in the enlarged lymph nodes in different parts of the body showed a diffuse overproduction of lymphocytes, arranged in an inconspicuous stroma of connective tissue. The histologic changes in the enlarged spleen were those of chronic passive congestion.

Case IV.—A. B., a negress, aged thirty-one years, was admitted to Bellevue Hospital November 25, 1925, complaining of dyspnea which, she said, had commenced suddenly four weeks previously. The patient stated that it was becoming increasingly difficult for her to breathe, but she complained of no pain or cough.

At the time of admission, she was orthopneic and physical examination revealed swelling of the right upper extremity and of the corresponding breast. Expansion was absent over the entire right chest. Fremitus was absent below the fourth dorsal spine, beneath which there was flatness with distant bronchial breathing and egophony and, above this, Skodaic resonance and impure bronchial breathing. The left chest was hyperresonant. The heart was displaced to the left, the apex resting in the sixth interspace, 16 cm. from the midline. No heart sounds could be heard. Palpation of the abdomen was negative and there was no enlargement of the superficial lymph nodes. Shortly after admission the right chest was tapped and 1480 cc. of clear fluid were removed. In the course of the next three weeks, the right pleural cavity was tapped on five occasions, yielding a total of 9000 cc. In spite of the removal of fluid, however, dyspnea not only continued but became more distressing and finally death supervened.

Autopsy. On lifting the sternum, an enormous tumor came into view lying in the region normally occupied by the thymus. The growth, which measured 15 cm. in length and 8 cm. in breadth, approximated the shape of the normal thymus to a noticeable degree. Anteriorly, the tumor was attached to the posterior surface of the sternum, and on the right side, at the third and fourth interspaces, it penetrated and replaced the intercostal muscles over a wide area. Posteriorly the growth extended as far as the root of the lung, molding itself around the great structures of the upper portion of the thorax—the aorta, trachea and larger bronchi, and the origin of the carotid arteries. Laterally, the tumor infiltrated practically the whole of the parietal pleura on the right side, so that the pleura was thickened to the extent of from 3 mm. to 1 cm., the infiltrating neoplasm presenting a smooth or somewhat undulating surface, with here and there

nodular formations, the largest of these being about 1 cm. in diameter at the base. The tumor at its lower extremity presented a notch which was about 3 cm. in length, thus dividing the growth into two poles—a right and a left. The right pole extended downward over the pericardium and brought about infiltration of the diaphragmatic pleura, which was thickened from 1 to 4 cm. The left pole sent prolongations from its posterior aspect directly through the upper portion of the pericardium, and the intrapericardial portions of the aorta and the origin of the pulmonary artery were infiltrated with nodular tumor tissue, while on the anterior surface of the right auricle, at about its center, was a solitary nodule fixed to the wall of the auricle by a base which measured 1 cm. in diameter, the mass itself being about ½ cm. in height and mushroom shaped. In the epicardium, corresponding roughly to the course of the left coronary artery, were about a dozen pinhead sized or slightly larger tumor deposits, and in the wall of the left ventricle laterally, midway between apex and base, were two or three nodules, the largest measuring about 1 cm. in diameter at the base. In an upward direction, the growth extended to the level of the sternum, but did not infiltrate the structures of the neck. Posteriorly, lying just in front of the spinal column and extending downward as low as the pillars of the diaphragm, were numbers of tumor nodules, directly continuous with the main growth already described. The right lung was compressed, partly by the tumor itself and partly because of the presence in the pleural cavity of a collection of about 750 cc. of serous fluid. The left pleura was free. The spleen was normal in size and presented a half dozen small capsular nodules which, on section, extended downward into its substance for a few millimeters. The left kidney, immediately beneath the capsule at the upper pole, showed two or three small whitish deposits flush with the surface of the organ and extending downward into its substance for a distance of from 3 to 6 mm.

Microscopic examination of sections removed from the mass in the thymic region revealed a densely cellular growth of lymphocytes arranged diffusely in an inconspicuous stroma. The same histologic appearances obtained in the enlarged lymph nodes, and there was an identical infiltration of the pleura and the heart muscle.

Case V.—The patient was a boy, aged seventeen years, who, on admission to Bellevue Hospital, said that two weeks previously he suddenly became short of breath and was seized by a dull pain in the upper part of the chest, attended by cough and expectoration.

On physical examination, both legs were edematous and the face and neck were cyanotic. On percussion of the chest, there was marked flatness from the clavicles downward. Thoracentesis was followed by the withdrawal of enormous amounts of fluid. The abdomen was similarly distended. The urine showed a trace of albumin, but no casts.

Autopsy. On opening the thorax, both pleural cavities were found to contain large quantities of fluid, compressing the lungs, which were displaced upward. Lying in the anterior mediastinum, corresponding to the position of the thymus, was a large, firm mass which extended upward as far as the lower level of the neck and downward in front of the pericardium to the level of the auriculoventricular groove. The pericardium was distended by fluid and strewn over both layers was a sheeting of fibrinous exudate. The heart muscle in the upper part of the left ventricle was fleshy in appearance, as if infiltrated by tumor growth. Both kidneys were enormously increased in size, each measuring 15 by 10 by 7 cm. and weighing, together, 1040 gm. The form was well preserved and the surface was pale, the cortex broad, fleshy, the markings obscured. The retroperitoneal and lower cervical lymph nodes were moderately enlarged and the bone marrow presented numbers of whitish foci.

Histologically, sections from the growth in the region of the thymus showed diffuse proliferation of lymphocytes with scarcely any discernible supporting framework, but with a liberal supply of small vascular channels. Practically identical changes were present in the lymph nodes. On the surface of the visceral pericardium was a thick layer of densely packed lymphocytes, among which were many thin-walled bloodvessels, while superimposed was a stratum of fibrinous exudate. Among the underlying heart muscle fibers scattered foci of lymphocytes were to be seen. The bone marrow exhibited patchy infiltration of the same sort of cells.

CASE VI.—G. U., aged thirteen years, was admitted to Bellevue Hospital in July, 1923, complaining of weakness and pain in the left side of the chest of two weeks' duration. The onset, he said, was sudden and accompanied by cough and a feeling of fatigue.

On admission, the skin and visible mucous membranes were pale and the patient was markedly dyspneic. The left side of the chest bulged noticeably and diminished respiratory movements on that side were accounted for by signs of fluid in the corresponding pleural cavity, the heart being displaced to the right. There was slight general lymphadenopathy. The spleen and liver were not palpable and there were no detectable masses in the abdomen. Thoracentesis was performed four times and a total of over 2000 cc. of blood-stained fluid was removed from the left chest.

On August 8, 1923, slightly more than a month after admission, it was noticed that the spleen was palpable 10 cm. below the costal margin and that a small subcutaneous nodule, which previously had been present beneath the skin of the left chest, had disappeared. The patient became progressively weaker and hemorrhages occurred into the mucous membrane of the uvula and the inside of the cheek. The liver was now at a level with the umbilicus, and the lower edge of the spleen reached the pelvis. Ecchymosis occurred in the left pectoral muscle, and purpuric spots appeared around the joints of the elbows, wrists, ankles and knees. On admission, the white blood cells numbered 22,000, of which 50 per cent were polynuclear neutrophils, 46 per cent lymphocytes and 4 per cent mononuclears. The blood count on July 26 showed an increase of lymphocytes to 61 per cent, and on September 7 the white cells numbered 97,600 and, of them, 98 per cent were lymphocytes.

Autopsy. The body was that of an emaciated, very anemic boy, in whose conjunctivæ and skin there were numerous petechial hemorrhages, together with crusted blood about the gums. Both pleural cavities were distended by blood-stained fluid. In the anterior mediastinum, corresponding to the position normally occupied by the thymus, was a massive tumor, which extended downward from the jugular fossa to the level of the crura of the diaphragm and posteriorly to the spinal column, molding the aorta, pulmonary artery and trachea into its substance. The growth was firm in consistence and, on section, showed areas of whitish tissue intermingling with reddish streaks or dots. On the left side, it brought about extensive infiltration of the diaphragm and of the pleura in the region of the apex of the left lung, the pleura in this situation being thickened and nodular. The liver was enlarged and studded with minute whitish areas. The submaxillary lymph nodes on the left side were markedly enlarged, as were the axillary and inguinal nodes on both sides, and the mesenteric nodes, all of them discrete and fairly firm to the touch. The spleen was increased in size, weighing 350 gm., but, on section, showed no indications of tumor growth. There were numerous petechial hemorrhages in the epicardium, in the mediastinal tumor itself, and in many of the lymph nodes.

Microscopic sections from the growth in the thymic region and from lymph nodes in various parts of the body showed thickly cellular lymphocytic collections supported by an almost imperceptible stroma of connective

tissue with, in both situations, a sprinkling of small injected bloodvessels. Sections from the pleura revealed infiltration of its walls by hordes of lymphocytes, the underlying alveoli being compressed. In the diaphragm the muscle fibers were widely separated by myriads of similar cells, in other places the muscle tissues were completely replaced by them. In the liver were large and small interstitial and intralobular collections of lymphocytes, together with the intrusion of many lymphocytes into the blood of the sinusoids.

CASE VII.—L. G., aged thirty-eight years, a clerk, was admitted to Bellevue Hospital December 2, 1924. Little could be learned of his history, except that for two weeks past he had complained of cough and precordial pain.

At the time of admission, physical examination revealed a mass of enlarged lymph nodes in the left submaxillary region, 5 cm. in diameter. The left posterior cervical nodes were enlarged, forming a mass 10 by 5 cm. Enlarged lymph nodes were present in both axillæ, those in the right forming a mass about 4 cm. in diameter. The inguinal lymph nodes were moderately enlarged. All of the nodes were discrete and movable. The liver was not felt. The spleen was palpable on deep inspiration under the costal margin in the anterior axillary line.

During the twenty-seven days that the patient was under observation, petechiæ appeared in various parts of the body and, on the ninth day, there was bleeding from the nose. The temperature for the first twelve days pursued an irregular course, averaging 102.5° F. in the evening. For the next six days, it varied from 100° to 101° F. and finally became septic in type. The patient now complained of sweats, cough and intermittent dyspnea. On the second day after admission, the blood count revealed 14,400 leukocytes, with a differential count of 9 per cent polynuclear neutrophils and 91 per cent immature lymphocytes. All subsequent counts were virtually the same. The left chest was tapped on three occasions for a total of some 3500 cc. of fluid.

Autopsy. On opening the chest, the anterior mediastinum was found to be completely occupied by a firm wedge-shaped tumor which measured 12½ by 6 cm. and which was attached to the lungs on both sides. On section, the mass consisted largely of white or cream-colored, rather firm, glistening, homogeneous tissue. On the left, an extension ran downward over the anterior surface of the pericardium as far as the diaphragm and infiltrated the pericardium and the anterior margin of the left lung. Lymph node enlargements were encountered in the neck, axillæ and groins, as mentioned in the clinical history, and there were one or two slightly enlarged nodes in the retroperitoneal region. The rest of the lymphatic system, including the spleen, showed nothing worthy of note.

Microscopic sections from the mass in the region of the thymus showed a densely cellular growth of lymphocytes in which the cells were arranged in islands of variable shape and size, but in which streaklike formations occurred with striking frequency. In the lymph nodes the lymphoid cells stained rather less intensely and tended to follow a more diffuse arrangement. In the spleen were numbers of moderately hyperplastic lymphoid follicles, together with a sprinkling of lymphoid cells and fairly numerous lymphocytic clusters lying in the sinuses, the appearance of the spleen as a whole being considerably more cellular than in ordinary circumstances. In the liver were to be seen minute aggregations of lymphocytes, particularly in the interstitial connective tissues and many lymphocytes in the blood of the sinusoids.

Lymphosarcoma of the Gastro-intestinal Tract. CASE VIII.—The patient, a man aged fifty years, was admitted to Bellevue Hospital with signs of

cardiac decompensation. The urine contained a trace of albumin and a few hyaline and granular casts. Beyond this, the physical examination revealed nothing worthy of note in the present connection, and the patient's history was negative, except for the fact that he complained of nothing referable to disturbances in the gastro-intestinal tract.

Autopsy. The middle of the jejunum presented two infiltrated whitish elevations, 4 cm. in diameter, extending around the intestine bracelet-fashion. They were separated from one another by several centimeters of healthy mucosa. A similar circumferential infiltrated band, 1 cm. in diameter, was found in the middle of the ileum, the center of the band, corresponding to the mesenteric attachment, being ulcerated. Microscopic examination of the ulcerated area in the intestine showed dense lymphocytic infiltration of the submucosa, together with the insinuation of richly cellular lymphocytic columns between the muscle bundles of the inner circular layer. The kidneys were markedly enlarged and weighed, together, 630 gm. They were yellowish-white and, on section, the cortices were broadened and the markings obliterated by cream-colored tissue. Microscopic examination revealed enormous numbers of lymphocytes invading the intertubular spaces from cortex to pelvis. The glomeruli and the tubular epithelium appeared to be intact.

Comment. This case is interesting in that multiple ulcers of the gut were present without any symptoms whatsoever referable thereto. Furthermore, there was extensive infiltration of both kidneys and no urinary changes except a trace of albumin and a few hyaline and granular casts.

Case IX.—E. R., aged fifty-six years, a salesman, was admitted to Bellevue Hospital November 9, 1916, with signs of cardiac decompensation. There was nothing in the clinical history to indicate any disturbance of the gastrointestinal tract.

Autopsy. Autopsy revealed an indurated ulcer lying in the ileum, about 15 cm. from the ileocecal valve. The edges of the ulcer were sharp and the gut in the immediate vicinity, for a distance of about 1 cm. in all directions, was thickly infiltrated by whitish tumor material. Higher up in the ileum and jejunum were several smaller whitish, submucous areas of infiltration, without evidences of ulceration. The retroperitoneal lymph nodes were enlarged, varying in diameter up to 5 cm. and, on section, presented a whitish homogeneous appearance. The superficial lymph nodes and those in the chest were free. The spleen was enlarged, weighing 515 gm. and presented the customary naked eye and microscopic appearances of chronic passive congestion.

Microscopic examination of tissues from the ulcerated area in the intestine showed a richly cellular aggregation of lymphocytes lying in the remnants of the mucosa, distending the submucosa to a marked degree and filtering through the interstices of the muscle tissues to the subserous spaces.

Comment. This case is worthy of note as showing the occurrence of multiple lymphosarcomatous foci in the wall of the gut, with nothing in the patient's clinical history to indicate disturbances arising therefrom. It further serves to emphasize the observation that enlargement of the spleen in association with lymphosarcoma is oftenest traceable to some independent factor—in this instance to chronic passive congestion secondary to cardiac decompensation.

Cases X and XI are of anatomical interest only, since in neither is the clinical history available.

Autopsies. The first of the two concerned a man, aged fifty years, in whom, at autopsy, was found, in the left half of the transverse colon, a new growth which was firm in consistence, grayish-white in color and which infiltrated the wall of the gut in circular fashion for a distance of about

1 cm., raising the mucosa, the surface of which was superficially ulcerated. In the sigmoid there was a new growth, likewise circularly arranged, although not completely surrounding the gut, measuring 5 cm. in length and presenting essentially the same naked-eye appearances as the one just described. Otherwise the organs revealed nothing worthy of note in this connection, the lymph nodes throughout the body being entirely free.

Microscopic examination of tissues removed from the ulcerated area in the intestine revealed a dense infiltrate of lymphocytes lying largely in the submucosa, but invading the deeper muscle tissues.

The second case concerned a man, aged thirty-four years, who at autopsy showed in the small intestine several large and small masses, the largest approximating 8 cm. in diameter. The mucous membrane covering these masses was, in places, superficially ulcerated, in other places intact. In the ascending colon, in addition, was a large tumor, superficially ulcerated and presenting the same naked-eye appearance as those just referred to. Here, again, the lymph nodes throughout the body were intact.

Microscopic examination of tissues from the ulcerated areas in the intestine showed a densely cellular lymphocytic growth, the lymphocytes infiltrating the intertubular spaces and insinuating themselves between the muscle bundles, but appearing most prominently in the form of dense hordes lying immediately under the serosa.

Lymphosarcoma of the Lymph Nodes. CASE XII.—J. A., a housewife, aged forty-two years, married, was admitted to Bellevue Hospital October 11, 1916, slightly dyspneic and jaundiced, with shifting dullness in the flanks and a fluid wave. A distinct mass was felt in the epigastric region, firm to the touch and somewhat tender. The spleen was palpable about 4 cm. below the costal margin. Soon after admission, the patient developed a friction rub which could be heard over the entire precordium, together with a friction rub over the lower lobe of the right lung, followed by signs of fluid in the corresponding chest. The patient, who was now deeply jaundiced, had been growing gradually weaker, particularly since the onset of the signs of pericarditis, and complained of considerable pain in the region of the heart. Death occurred on the seventeenth day.

Autopsy. Autopsy revealed the body of a markedly jaundiced female. On section, 7 liters of dark-yellow, serous fluid were released from the abdomen. On opening the chest, about 480 cc. of clear serum were detected in the right pleural cavity and the corresponding lung was compressed. Scattered over the layers of the pericardium were quantities of fibrinous exudate. On opening the abdomen, a huge tumor was found in the retroperitoneal region, lying in front of and to the side of the spinal column and extending downward into the pelvis. It was made up of numerous hyperplastic lymph nodes, varying in diameter from 1 to 5 cm. and presenting, on section, a homogeneous, glistening appearance. There was no enlargement of the lymph nodes in any other part of the body. The spleen weighed 470 gm. and presented the naked eye changes incident to chronic passive congestion.

Microscopic examination of the enlarged lymph nodes showed a diffuse, densely cellular growth of lymphocytes.

Comment. This case is remarkable as an example of massive lymphosarcoma restricted to the retroperitoneal lymph nodes, but expanding locally in such fashion as to interfere with the portal circulation and with the escape of bile, producing ascites on the one hand and jaundice on the other. Interesting also is the fact that the spleen was palpable during life, the enlargement having been shown, at autopsy, to be due to chronic passive congestion, most likely following mechanical interference with the circulation of the splenic vein caused by compression from the tumor growth. It is another concrete example of the rule that enlargement

of the spleen in association with lymphosarcoma is usually to be ascribed to secondary factors and not to changes in its native lymphoid elements. Furthermore, the case is worthy of note in that the intraäbdominal tumor, which, incidentally, was not accompanied by lymph node enlargements in any other part of the body, gave rise during life to signs which were strongly indicative of cirrhosis of the liver, namely, jaundice, ascites and slight enlargement of the spleen.

Case XIII.—E. G., aged forty years, was admitted to Bellevue Hospital in April 1925, complaining of nodular enlargements on both sides of the neck and in the axillæ and groins, attended by enlargement of the abdomen and progressively increasing weakness, all of some three months' duration. The blood count was normal. The patient was given a series of Roentgen ray exposures, and the lymph node enlargements improved remarkably. She left the hospital, but was readmitted about eight months later with the symptoms and signs of croupous pneumonia, dying seven days after admission.

At the time of her second admission, physical examination revealed enlargement of the lymph nodes of the neck on both sides, marked enlargement of the nodes in the axillæ, and moderate enlargement of those in the inguinal region. The liver was palpable. The spleen was felt two fingers' breadth below the costal margin on the left side. The blood count was normal, except for a moderate degree of secondary anemia.

Autopsy. Autopsy showed, in addition to enlargement of the superficial nodes as outlined in the clinical history, enormous numbers of enlarged abdominal nodes, particularly in the region of the hilum of the liver, around the head of the pancreas, and in the retroperitoneal region and mesentery. The individual nodes were grayish in color, homogeneous in appearance, and varied from $1\frac{1}{4}$ to 5 cm. in diameter. On microscopic examination, they revealed closely packed hordes of lymphocytes growing diffusely. The spleen weighed 610 gm. and was firm in consistence and congested, and, on microscopic examination, showed marked congestion and diffuse hyperplastic changes in the lymphoid follicles, the increase involving the small lymphocytes exclusively, no germinal areas being seen.

Case XIV.—F. McC., a teamster, aged fifty years, was admitted to Bellevue Hospital November 12, 1917, with the statement that nine months previously he noticed that his abdomen was enlarging and that he experienced some difficulty in breathing and that his feet were swollen. He finally became so weak that he had to stop work and was admitted to St. Vincent's Hospital, where he was tapped and a large quantity of fluid removed from the abdominal cavity. There was nothing of further interest in the patient's history, except for the fact that he admitted having had a chancre twenty-two years previously and that practically all of his life he had been addicted to the inordinate use of alcohol.

At the time of admission to Bellevue Hospital, the patient complained of swelling of the abdomen, dyspnea, nausea and vomiting. On the day of admission, he was tapped and a huge quantity of amber fluid was removed from the abdominal cavity. Examination revealed no enlargement of the superficial lymph nodes. In the anterior abdominal wall were numbers of dilated superficial veins. The patient became progressively weaker and died on the eighth day after admission.

Autopsy. Imbedded in the fat tissues of the mesentery and lying in the retroperitoneal region around the aorta and inferior vena cava, were immense numbers of enlarged lymph nodes, the individual nodes varying in size from 2 to 9 cm. They were rather firm, elastic to the touch, yellowish white in color and, on section, presented a smooth, glistening, homogeneous appearance and were arranged discretely, but were closely packed. The

spleen weighed 365 gm. and was firm in consistence, showing, on microscopic examination, a somewhat cellular interstitial splenitis, most likely syphilitic in origin. Except for the presence of a few small whitish nodules in the wall of the left ventricle, the rest of the organs showed nothing worthy of note.

On microscopic examination, the lymph nodes were characterized by diffuse hyperplasia of lymphoid cells lying in a stroma which, in places, was thickened and hyalinized, the latter changes most probably to be ascribed to syphilis.

Comment. This case, like the one preceding, is notable in that the tumor growth was localized practically exclusively within the abdomen and that, as a result of pressure, it served to bring about obstruction to the outflow of bile, eventuating in jaundice and interference with the portal circulation, producing ascites, and these signs, together with the patient's admission of syphilis and of inordinate addiction to the use of alcohol, together with the presence in the anterior abdominal wall of dilated veins, naturally diverted suspicion in the direction of cirrhosis of the liver.

CASE XV.—N. H., aged fifty years, a seamstress, was admitted to Bellevue Hospital May 23, 1919, complaining of enlarged lymph nodes in various parts of the body that had been present for a period of five years and which, in the course of the past three years, had been slowly increasing in size. The patient stated that, just previous to her admission to the hospital, she had suffered on occasions from precordial pain.

Physical examination at the time of admission revealed a poorly nourished woman with rapid and labored respirations, hoarse voice and cyanosis of the lips. Over the chest anteriorly were numbers of dilated veins, more marked on the left side. The liver and spleen were not felt. The lymph nodes on both sides of the neck were massively enlarged. The inguinal lymph nodes on either side formed masses from 12 to 15 cm. in length and about 4 cm. in diameter, and the axillary lymph nodes were likewise greatly enlarged. The nodes were discrete and varied in size. Both legs were markedly edematous. Physical examination of the chest revealed dullness over the upper lobe of the right lung anteriorly, most marked close to the sternum, together with diminished breath sounds. Below the angle of the scapula on both sides were diminished breath sounds and fremitus, and many fine moist râles, particularly on the left. During her stay in the hospital, the patient's left chest was tapped at intervals of a few days on six occasions for a total withdrawal of 3300 cc. of fluid, and the right chest was tapped eight times for a total of 5700 cc.

Autopsy. Autopsy revealed a markedly emaciated body, showing massive enlargement of the superficial lymph nodes, as described in the clinical history, the skin over the nodes being freely movable, while the nodes themselves were fixed to the deeper structures. The anterior portion of the chest, from the level of the thyroid to the diaphragm, was crowded with innumerable closely packed lymph nodes, varying in size from a few millimeters to several centimeters. The growth of lymph nodes extended directly backward, surrounding the great vessels at the base of the heart and the trachea, and infiltrating directly through the pericardium into the right auricle of the heart, appearing on the inside as a mushroom-like mass. The pleura covering the left lung was greatly thickened and uniformly infiltrated throughout. The right pleura was free. In the abdomen, immense masses of enlarged lymph nodes were found around the pancreas and at the hilum of the liver and in the mesentery. The spleen was described as somewhat enlarged.

Microscopic examination of lymph nodes removed from different areas showed a uniform picture in the form of a dense growth of lymphocytes with scanty supporting stroma and a rather rich supply of small blood-

vessels. The heart muscle was extensively infiltrated and replaced by lymphocytes, and numbers of localized and diffuse collections were to be seen in the interstitial tissues of the kidney.

Comment. This case represents, anatomically, the most extensive involvement of any one in the entire series, the predominant lesions being found in the lymph nodes of the chest, although those of the abdomen pursued as a close second, while the superficial lymph nodes were likewise enlarged in massive proportions. Clinically, the case furnishes still another example of the remarkable facility with which the several organs of the body adapt themselves to gradually increasing pressure, as evidenced in this case by enormous overgrowth of lymph nodes in the chest that must have been present for many months, without any complaint from the patient other than occasional precordial pain, followed later and suddenly by difficulty in breathing, the advent of these signs preceding death by a few weeks only.

CASE XVI.—L. M., aged sixty-three years, had been operated on and an enormous mass of lymph nodes removed from the right side of the neck. No blood changes were present during life. *At autopsy*, all the organs were intact.

Histological examination of the lymph nodes removed surgically revealed a diffuse growth of small lymphocytes.

Lymphosarcoma of the Prostate. CASE XVII.—The patient was a man, aged thirty years, born in Denmark, and from whom a satisfactory history could not be obtained. It was learned, however, that in the course of the seven weeks previous to admission, he had lost twenty pounds in weight and that he complained that it was frequently necessary for him to void urine, and that on one occasion he had great difficulty in passing it for a period of several days.

Autopsy. At autopsy, the region of the prostate was occupied by a growth that measured 9 cm. in diameter and 7 cm. in length. It surrounded the posterior urethra and was continuous with the lower third of the bladder in which locality the walls of the bladder were thickened to the extent of about 1 cm. and, on section, presented the same pale, smooth, cream-colored appearance as the cut section of the tumor in the prostate proper. The thickening of the bladder wall gradually disappeared as the viscus ascended into the pelvis, so that at the fundus it was about normal. Laterally the growth from the prostate directly invaded the psoas magnus muscles on both sides, while strewn along the front of the spine from the brim of the pelvis upward as far as the level of the pancreas, were numbers of large and small, rounded, oval or flattened nodules, some of which were discrete, others fused, and which presented, on section, much the same appearance to the naked eye as the tumor in the prostate. The ureters on both sides ran directly through these masses. In the pleura of the left side was a small cream-colored nodule.

Histologic examination of the prostate showed widespread replacement by a growth of lymphocytes arranged diffusely or in islands of variable shapes. The enlarged abdominal lymph nodes showed similar changes. The ureters and psoas muscles were richly invaded by lymphocytes and numerous foci of identical cellular composition were present in the liver.

Comment. Lymphosarcoma of the prostate, as far as I have been able to learn, is an extremely rare disease.[3] It has been shown, however, that the prostate belongs to the auxiliary lymphoid system, that is to say, that, with the suprarenal capsule, thyroid, lung, liver, kidney, testicle and other organs, the prostate normally contains minute interstitial lymphoid foci which in ordinary circumstances are apt to be overlooked, but which in certain conditions of disease are readily identified. There is no apparent reason, therefore, why a tumor of lymphoid cells should not spring from

such a focus in the prostate nor, indeed, why any one or all the members of this group of organs should not react similarly. That they do not more commonly give rise to lymphocytic growths is to be explained by the fact that the lymphoid rests in them are numerically insignificant and functionally dormant, undergoing hyperplasia only in unusual circumstances, whereas the follicles of the lymph nodes, tonsils, gastrointestinal tract, and so forth, are distributed in such fashion as to serve as filters, in which capacity they are constantly engaged in the process of compensatory regeneration and, hence, are frequently subject to physiologic variations of cell equilibrium, between which and neoplasia the dividing line is thin.

Distribution and Incidence. In a collated series of 100 cases, recorded by Kundrat,[1] Ghon and Roman,[4] MacCallum,[5] and myself, lymphosarcoma occurred in the situations and to the extent shown in the following table:

DISTRIBUTION OF LYMPHOSARCOMATA.

Site.	Number.
Gastro-intestinal tract	36
Thymic remains	21
Cervical nodes	14
Abdominal nodes	11
Pharynx	7
Tonsil	3
Mouth	2
Inguinal nodes	2
Spleen	1
Axillary nodes	1
Thoracic nodes	1
Prostate	1

Unfortunately, I have not been able to collect data having to do with the comparative frequency of lymphosarcoma and Hodgkin's disease. My impression, however, is that Hodgkin's disease is by far the commoner. I am conscious of no exaggeration when I say that I have seen Hodgkin's disease and lymphosarcoma in living patients in the wards of Bellevue Hospital in the proportion of at least 12 to 1, in all of them the diagnosis having been arrived at by histologic examination. On the other hand, autopsy statistics from the same institution indicate their occurrence in almost identical numbers—17 cases of lymphosarcoma and 16 cases of Hodgkin's disease in 11,925 autopsies.[10] I am aware that autopsy statistics, as accumulated in this country, while valuable, do not represent a transection of the sick community and, in like manner, that personal impressions are not exempt from assault.

The Individual Tissue Changes in Lymphosarcoma. *The Lymph Nodes.* Primary involvement of the lymph nodes occurred in this series on 5 occasions. In 1 case there was massive unilateral enlargement of the cervical nodes and the other organs were intact. In a second case the intrathoracic lymph nodes were enlarged in countless numbers and were associated with extensive changes in the abdominal nodes and massive enlargement of all of the super-

ficial groups. In 3 cases the abdominal nodes were primarily concerned.

The superficial lymph nodes were unchanged in six instances—twice in lymphosarcoma of the abdominal nodes, twice in primary growths in the gastrointestinal tract, once in primary lymphosarcoma of the thymus, and once in lymphosarcoma of the prostate. In the remaining cases the superficial nodes were enlarged to a variable degree, attaining marked proportions, however, oftener than otherwise.

The Thymus. In 7 of the 17 cases in this series (41 per cent), lymphosarcoma was found arising from the lymphoid remnants of the thymic body, as revealed by massive solid growths lying in the anterior mediastinum in the position normally occupied by the thymus and not uncommonly feigning its shape, sometimes to a remarkable degree. According to the evidence afforded by the comparatively small series of cases here recorded, it is the commonest variety of lymphosarcoma. The figure is somewhat misleading and represents an unusual individual experience rather than a fair estimate of the incidence of thymic lymphosarcoma. Nevertheless, that it is by no means uncommon in the experience of others is shown by the combined statistics which appear in this paper and which indicate that it ranks second in point of frequency.

Important in this connection is the fact that Hodgkin's disease is capable of originating a growth in the thymic body that, clinically and anatomically, may counterfeit primary thymic lymphosarcoma to the last detail, although histologically the two are usually separable, Hodgkin's disease of the thymus presenting a histology identical with that of the lymph nodes, spleen and elsewhere. There is a total of but 6 detailed cases of thymic Hodgkin's disease to be found in the literature—1 by Yamasaki,[6] a second by Chiari,[7] a third by Lyon,[8] 1 by Wollstein and McLean[9] and 2 by myself.[10] In addition, Simonds,[11] in a review of the literature of Hodgkin's disease, refers casually to an instance which came under his observation. At the time of the present writing, there are 2 patients in the wards of Bellevue Hospital, in both of whom microscopic examination of an excised lymph node shows the histology of Hodgkin's disease, and in both of whom the Roentgen ray reveals an enormous, apparently solid tumor growing in the region normally occupied by the thymus. Although these observations indicate that the incidence of thymic Hodgkin's disease is not high, the condition suffices to command a place in any discussion which has to do with tumors and tumor-like growths of the thymic remains.

Anatomically, lymphosarcoma of the thymus and its companion lesion in Hodgkin's disease form an alliance either member of which is able to bring about destructive changes in the thoracic viscera to a measure almost unparalleled in the domain of disease—penetration of the pericardium and invasion of the heart muscle, infiltra-

tion of the pleura over a prairie-like expanse, invasion and compression of the lungs, infiltration of the esophagus, trachea and bronchi and of the walls of such great vessels as the aorta, pulmonary artery and superior vena cava, and often by enlargement of lymph nodes in parts of the body that are widely remote from the parent growth, together with secondary effects as revealed by the transudation of fluid into the pericardial and pleural sacs and the peritoneum and subcutaneous tissues. As illustrating the astonishing adaptability of tissues to incursions of this sort, it not uncommonly happens that the living patient carries this burden of disease for many months without complaint or obvious signs of suffering. Of the 7 cases of thymic lymphosarcoma outlined in this paper, 6 complained of symptoms referable to increased intrathoracic pressure coming on "suddenly" and followed not long thereafter by death, whereas the anatomic changes in the thoracic viscera were such as to indicate a period of growth extending over months or even longer. At the moment of writing, there is, as mentioned above, a patient under treatment at Bellevue Hospital in whose thymic region the Roentgen ray discloses an enormous growth, numerous masses are to be palpated in the abdomen and the superficial lymph nodes are enlarged to a marked degree. Examination of an excised node shows the histology of Hodgkin's disease. The patient complains of no pressure symptoms referable to the chest, but rests in complete comfort. Similar examples are to be quoted from the literature. The epithelioma of the thymus recorded by Rubaschow[12] produced extensive destructive changes in the thorax without a single sign during life to be attributed to intrathoracic pressure. In a case of massive epithelioma of the thymus, described by Symmers and Vance,[13] attended by widespread invasion of the intrathoracic structures and metastatic deposits in the vertebræ, the patient, except for pain on swallowing, at no time exhibited signs or complained of symptoms attributable to abnormal pressure within the chest. In 1 of Sternberg's[14] cases, clinical disturbances were said to have been of three weeks' duration, but the intrathoracic tumor was of enormous size and, according to Sternberg, must have been in existence for a period greatly in excess of that suggested by the clinical history. In a case recorded by Wollstein and McLean,[9] the patient, a child, was mildly dyspneic, but a mediastinal growth was not suspected during life and its discovery at autopsy came as a surprise.

In 2 of the cases of primary thymic lymphosarcoma in this series, the patients succumbed to the effects of an acute leukemia—the so-called lymphoid leukosarcomatosis, a term which Sternberg introduced to denote a disease characterized by the long-standing presence in some part of the body of a growth composed of lymphoid cells. These cells, for no apparent reason, are suddenly poured into the blood in large numbers and life terminates with the picture

of acute leukemia. In his paper, Sternberg records 8 cases, in 4 of which the original growth was located in the mediastinum corresponding to the position of the thymus body. Since the appearance of Sternberg's paper, the literature has been considerably enriched and cases of leukosarcomatosis have been recorded in this country and elsewhere, not only in association with lymphosarcoma of the thymus gland, but with lymphoid tumors in other parts, among them, the stomach, breast, the cervix of the uterus and the lymph nodes of the neck.[15]

The Spleen. In 7 of the 17 cases of this series (41 per cent), the spleen was enlarged. The recorded weights in 6 were 470, 350, 515, 610, 448 and 365 gm.—an average of 459 gm., or 309 gm. in excess of the normal. In the remaining case, the enlarged spleen measured 15 by 8 cm., but its weight was not noted. In 4 cases, the enlargement was due to chronic passive congestion, dependent on defective heart action or on local obstruction to the outflow of blood brought about by the pressure of enlarged lymph nodes within the abdomen. In 1 case, histologic examination of the enlarged spleen revealed an interstitial splenitis occurring in a syphilitic subject. In the 2 remaining cases, microscopic examination of the spleen revealed diffuse hyperplastic changes in the follicles of a sort which suggested a local reaction to the provocative agent responsible for the lymphoid hyperplasia in other parts. In other words, in only 2 of the cases in this series (12 per cent) was it deemed justifiable to incriminate enlargement of the spleen as a part of the disease lymphosarcoma. The clinical value of these findings is not without significance in view of the fact that it is generally taught that splenomegaly is a frequent concomitant of lymphosarcomatosis. It is desirable, of course, to analyze a large series of cases, verified by biopsy or autopsy, to determine the diagnostic value of this sign. However, in 2 patients with generalized enlargement of the superficial nodes and splenomegaly whom I saw clinically —leukemia having been excluded and follicular lymphadenopathy with splenomegaly not then described—I ventured to suggest the probability of Hodgkin's disease rather than lymphosarcoma because of the presence of an enlarged spleen. In both cases, microscopic examination of an excised lymph node revealed lymphosarcoma. Conversely, in Hodgkin's disease, the spleen is known to be palpably enlarged in a notable percentage of all cases, but in those instances where it is normal in size or where splenomegaly, if present, is not clinically detectable, a diagnostic sign commonly regarded as of great value again loses something of its force.

Pericardium and Heart. Of the 17 cases in this series, the pericardium was infiltrated in 6 (35 per cent), five times in lymphosarcoma of the thymic remains and once in lymphosarcoma of the anterior mediastinal nodes, the invasion occurring directly and apparently because the pericardium offered a lesser line of resistance. In 5 of the 6 cases, penetration of the pericardium was followed by

invasion of the heart muscle. In 1 case the right auricle was practically completely replaced by tumor tissue. In a second, the growth extended through the right auricular wall and entered the cavity, where it expanded and grew mushroom fashion. In a third case, both auricles and the epicardial fat were widely infiltrated. In another, both ventricles were largely replaced, small, sheetlike areas of relatively well-preserved heart muscle showing through the tumor infiltrate at intervals. In still another case, there were a few small nodules in the wall of the left ventricle, while in the sixth case the intrapericardial portion of the aorta and the base of the pulmonary artery were richly studded with tumor nodules and there was a solitary nodule in the wall of the right ventricle and a few small nodules in the wall of the left ventricle, together with several minute foci in the epicardial fat. In short, in 4 of the 6 cases, the heart muscle was compromised in such manner and to such an extent as to occasion surprise that anyone could survive cardiac defects of the proportions indicated, the heart muscle thus affording an impressive example of the marvelous factors of safety which repose in this and many other tissues.

Pleura and Lungs. That the pleura is peculiarly vulnerable to invasion by lymphosarcoma is illustrated by the fact that in the present series it occurred six times (35 per cent). This is in contrast to involvement of the pleura in Hodgkin's disease where, in fifteen autopsies, I observed its inclusion in 1 instance only. In 1 case of the present series, both apical pleuræ were involved. In 3 cases the visceral pleura on one side was infiltrated throughout its extent, and in two of them the diaphragmatic pleura was equally implicated. In another case the whole of the left parietal pleura was infiltrated. In the remaining case there was a solitary nodule imbedded in the pleura on the left side. Five of these cases occurred in association with lymphosarcomatous lesions originating in the thorax—four times in thymic lymphosarcoma and once in lymphosarcoma of the intrathoracic lymph nodes, while the solitary nodule in the sixth case occurred in association with a primary growth of the prostate.

Miscellaneous Lesions. In 2 cases the esophagus was infiltrated, once diffusely and once in the form of a solitary nodule. One of these cases was associated with invasion of the walls of the superior vena cava and with almost complete lymphosarcomatous replacement of the pancreas, both occurring in association with a primary growth of the thymus.

The liver suffered comparatively little damage, showing numerous but small lymphoid foci in 3 cases.

In 2 cases the skeletal muscles showed widespread invasion, once in the form of direct penetration of the intercostal muscles from lymphosarcoma of the thymus, and in the other direct invasion of the psoas magnus muscles from a primary growth of the prostate.

In 5 cases the kidneys were involved, 2 showing minute but not numerous nodular foci in the cortex. In 3 cases, however, the

kidneys exhibited an extraordinary degree of enlargement due to diffuse infiltration by lymphocytes. In 1 of these the kidneys, together, weighed 1300 gm. and each measured 17 by 8½ by 8 cm.; in a second the organs, together, weighed 1040 gm. and each measured 15 by 10 by 7 cm. In both instances, the enlargement occurred in association with lymphosarcoma of the thymus. In a third case the kidneys, together, weighed 630 gm. and there was an attendant lymphosarcoma of the intestine.

The Nature of Lymphosarcoma. In certain quarters, lymphosarcoma is regarded as an infective process in which the tubercle bacillus is operative. Incidentally, the tubercle bacillus has been invoked from time to time as the cause of almost every disease to which the lymphoid system succeeds. As far as it is concerned in the causation of lymphosarcoma, there is little to support its claims more tangible than that of opinion. It has been demonstrated both clinically and experimentally that the tubercle bacillus can initiate a certain degree of lymphoid hyperplasia, but that it can sponsor a disease of such inordinate desires as lymphosarcoma is doubtful. The coexistence of lymphosarcoma and tuberculosis is often mentioned, oftener, I suspect, than it is verified, and is of questionable significance since there is no reason why the two should not share company. That attendant tuberculosis probably has nothing to do with the origin of lymphosarcoma is indicated, among other things, by the fact that, in the 17 cases of this series, the partnership was not noted in a single instance. In still other quarters, lymphosarcoma is regarded as a malignant neoplasm. This view has much to commend it. Nevertheless there are those who hold to an opposite opinion—that its tendency to infiltrate and destroy is no more pronounced than that of known infective diseases, among them, actinomycosis, and that the so-called secondary nodules which occur in various viscera do not constitute metastatic deposits dependent on the transplantation of cells from a parent growth, but result from the proliferation of lymphoid foci which are native to the tissues concerned. Finally, it is to be noted, again, that Hodgkin's disease and lymphosarcoma are capable in many instances of producing symptomatic disturbances and anatomic changes in the human body that are identical, and while Hodgkin's disease, for clinical purposes, may be regarded with equal fairness as a malignant process, there are arguments against including it among the true tumors that cannot be lightly set aside.

Summary. 1. Lymphosarcoma may implicate any of the lymphoid depots alone. It may bring about a diversified series of changes affecting tissues, lymphoid or otherwise, within more or less restricted territorial confines, or it may spread to include lymphoid and other structures over a wide geographical expanse.

2. Lymphosarcoma displays a predilection for the lymphoid tissues of the gastrointestinal tract, after which it seems to prefer the thymic remains as a place of operation. In the gastrointestinal

tract its activities are comparatively mild. Originating in the lymphoid remnants of the thymus, however, it is apt to bring about frightful destruction of neighboring tissues, featured by invasion of the pericardium and heart, by infiltration of the pleura and direct incursion into the lungs, by displacement of such mobile structures as the trachea, esophagus, aorta, pulmonary artery and vena cava, and sometimes by entrance into their walls, by penetration of the intercostal muscles and diaphragm, and finally by involvement of the lymph nodes, regional or remote, or both. It is an astounding, if ominous, fact that, in these circumstances, the changes enumerated may stretch themselves over an extended period without eliciting any complaint from the patient, and that both subjective and objective disturbances may be registered suddenly and without warning at a time when anatomic expansion has advanced beyond all hope of control.

3. Although from the clinical viewpoint lymphosarcoma bears an intimate resemblance to a number of other conditions affecting the lymphoid system, among them chronic lymphatic leukemia, pseudoleukemia, certain forms of lymph node tuberculosis and follicular lymphadenopathy with splenomegaly, Hodgkin's disease offers, perhaps, the widest range of similarities. While it is true that lymphosarcoma, notably its gastrointestinal forms, is capable of producing lesions that are unknown in Hodgkin's disease, in many other respects the two may impersonate one another to the minutest detail. Differentiation is to be accomplished only on the basis of excision and histologic examination of diseased tissue. Even in these circumstances confusion is possible, since in both conditions the initial changes in the lymph nodes are to be found in simple diffuse hyperplasia of the lymphoid cells, the nodes in Hodgkin's granuloma later assuming the complex histologic picture by which the fully established disease may be identified with certainty.

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THE ANGINAL SYNDROME IN PERNICIOUS ANEMIA.*

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Many years ago our attention was focused on the anginal syndrome of pernicious anemia by observing a patient who was admitted to the Clinic groaning with what he described as "severe agony in the chest." The agony varied in intensity but it continued until two transfusions had been given, when it disappeared. Since then we have observed many cases of pernicious anemia with less severe degrees of angina and our interest in the subject has led to a review of all of the cases of pernicious anemia seen by us in the last five years, with special reference to the occurrence of the anginal syndrome. Herrick and Nuzum, in 1918, alluded to the association of angina pectoris with pernicious anemia. Coombs has recently called attention both to the cardiac symptoms of pernicious anemia and to the anginal attacks that are seen in certain cases. Although angina pectoris has doubtless been observed by all who have had extensive experience with pernicious anemia, yet no comprehensive article on the subject is on record.

On observing patients with severe anemia one is frequently impressed with the remarkable degree of circulatory efficiency that is maintained. In order to maintain such efficiency, compensatory mechanisms are introduced which function variously in different cases. These compensatory factors have been studied by Fahr and Ronzone, who have shown that an increase in the minute volume of blood compensates for the diminution in the oxygen-carrying capacity of the blood. In their case of severe pernicious anemia (hemoglobin (Palmer) 12 per cent and 1,080,000 erythrocytes) the minute volume was increased about 250 per cent and the systolic output was increased proportionately. The blood viscosity was found to be lowered to 45 per cent of its normal value and to this change was attributed the increased velocity of the blood. The authors noted that the capillaries of the skin were contracted to half their normal diameter or less, and therefore concluded that the flow of blood through the skin was diminished and the flow through other organs increased.

After calculating the work of the heart (Evans' formula), Fahr and Ronzone concluded that the coronary circulation is taxed to

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the upper limit and is comparable to that in strenuous work. This observation implies that anoxemia of the heart muscle may readily develop in patients with severe anemia.

Analysis of Cases. Our study is based on the critical analysis of 1560 consecutive cases of pernicious anemia. No cases were included in which the diagnosis of pernicious anemia was uncertain. The anginal syndrome occurred in 43 of the cases (2.7 per cent).

Age and Sex Incidence. The average age of the patients with the anginal syndrome was 53.5 years. The youngest patient was twenty-four and the oldest sixty-seven years. It is of interest that 56 per cent of the cases occurred in the sixth decade of life. There was marked disproportion in sex incidence, 16 females (37 per cent) and twenty-seven males (63 per cent). The fact that women as a group are ordinarily not subjected to physical stresses and strains to the same degree as men may in part explain this discrepancy.

Cardiac Symptoms. The anginal syndrome occurred in relation to cardiac overload, especially as caused by physical exertion or eating a moderately large meal. Usually dyspnea and palpitation, and frequently tachycardia accompany the painful seizures. In 7 cases there was no actual pain; the patient complained of an oppressive sense of tightness and suffocation. The pain in most of the cases was retrosternal; in a few it was localized to the left of the sternum; it was described by the patient as "a tightness," "distress," "suffocation," "smothering sensation," "all gone feeling," or "agonizing pain." Occasionally the occurrence of sharp pain was described. In one instance pain was felt in the left side of the body. No case of abdominal angina occurred in this series. Radiation to the left arm was mentioned in two instances, to both arms in one, to the back of the neck and head in one, and to the throat in one. Only one patient suffered from a severe death-impending painful seizure; in this case the total duration of the anemia was a year and a half; no necropsy was available. None of the patients died in anginal attacks. In general the painful attacks are less severe and the radiation of pain far less frequent than in the anginal syndrome of primary cardiac disease.

Cardiac Findings. Slight but definite enlargement of the heart occurred in 12 of the 43 cases. No instance of extreme cardiac enlargement was noted. Murmurs were heard in most cases, systolic in time and blowing in character. The areas of maximal intensity and radiation were variable. Arrhythmia was rare, and when present was due to premature contractions, except for 1 case of auricular fibrillation. In 5 cases the heart sounds were of poor quality.

Duration of Symptoms of Pernicious Anemia. Definite information concerning the duration of the symptoms of pernicious anemia was obtained in 39 cases. In 33 cases the anemia had existed a year or more at the time of examination, in 18 of which it was known to

have been present two years or more. In 2 of the latter the diagnosis of pernicious anemia had been made eight years before. In only 6 cases had the duration of the disease been less than one year. The anginal syndrome is probably more prone to occur in cases of long duration.

Degree of Anemia. The hemoglobin readings and erythrocyte counts included in this study are the averages of two or more determinations. The hemoglobin in all cases was determined by the Dare method. The average hemoglobin was 35 per cent, the lowest reading being 10 per cent and the highest 68 per cent. The average number of erythrocytes was 1,780,000, the lowest number was 720,000, and the highest 3,370,000.

In 23 of 43 cases the red cell count was between 1,250,000 and 2,000,000 at the time of the patient's admission. In 7 cases the count was below 1,250,000, and in 3 of these below 1,000,000. In 2 cases the count was between 3,000,000 and 3,500,000. A rather marked degree of anemia was, therefore, present in most of the cases, but this can be considered only one probable factor in the production of anoxemia.

No definite constant relationship between the degree of anemia and the existence of the anginal syndrome was apparent. A study of the leukocyte and differential cell counts likewise failed to establish any relationship.

Blood Pressure. No unusual changes in blood pressure occurred in this group. The average systolic pressure was 124, the average diastolic pressure 71, and the average pulse pressure 56. It is interesting to note that in 40 of the cases the diastolic blood pressure varied between 50 and 75, while in only 3 cases were the readings below 50.

Electrocardiographic Findings. Electrocardiograms taken in 12 cases revealed no significant abnormalities. This observation agrees with that of Reid.

Pathologic Data. The record of only one necropsy was available in the group with the anginal syndrome. The diagnosis of pernicious anemia had been made five years before the death of the patient, a woman aged fifty-five years. Quite severe attacks of retrosternal pain on effort had occurred for a year and a half. These attacks disappeared after eight transfusions. Permission to remove organs was not granted but the heart was found to be small and apparently normal except for fatty changes in the myocardium.

Necropsy data were reviewed in 15 of the cases of pernicious anemia without the anginal syndrome. There were seven men and eight women. Their average age was 53.6 years. The youngest patient was thirty-eight, the oldest seventy years. The majority of them were in the later decades of life, 10 cases occurred in the sixth and seventh decades of life.

The weight of the heart was available in 13 cases. In 5 cases the weight was between 240 and 300 gm., in 3 between 300 and 400 gm., and in 4 between 400 and 500 gm. In 1 case the heart weighed 515 gm.

Marked sclerosis of the aorta and coronary arteries was observed in 3 cases. There were no other gross abnormalities. Histologic studies of the myocardium revealed fatty changes in 9 cases.

Comment. It is obvious that in pernicious anemia and other severe types of protracted anemia the heart is subjected to great strain in maintaining adequate ventilation of the tissues. The work of Fahr and Ronzone indicates the mechanisms by which efficiency of the circulation is maintained. The myocardium is undoubtedly often close to the margin of oxygen deficiency, and any overload, such as that induced by physical exertion, may readily produce a state of anoxemia of this important tissue. The anginal syndrome in pernicious anemia is in all probability due to the sudden and marked development of myocardial anoxemia.

Summary. Of 1560 patients with pernicious anemia seen since 1920, 43 (2.7 per cent) gave a history of angina. The average age of the patients was 53.5 years and 56 per cent of the patients were between fifty and sixty years of age. There were almost twice as many males as females. The anginal syndrome differed subjectively in no essential way from that of angina pectoris. Radiation of the pain was less frequent and agony was continuous in the severest cases of angina. The anginal syndrome occurred chiefly in cases of long duration. Objective examination of the heart showed no significant changes save those secondary to anemia. The degree of anemia did not bear a direct relationship to the occurrence of angina. Electrocardiographic examinations showed no significant abnormalities. In one necropsy only fatty myocardial changes were found. There was no aortic or coronary sclerosis. In 15 necropsies of other patients with pernicious anemia, the average age was fifty-three and only 3 showed aortic and coronary sclerosis. The anginal syndrome in pernicious anemia is due presumably to anoxemia of the myocardium and not to coronary or aortic sclerosis.

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AYERZA'S DISEASE.

With a Report of Two Cases.

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Ayerza's disease, which produces the black cardiac, the cardios negros of the Spanish, the cardiaque noir of the French, is due to a sclerosis of the pulmonary arteries often proved syphilitic in origin, and occurring as a sequel to a preceding chronic bronchitis. The outstanding clinical features are chronic cyanosis, dyspnea, erythrocytosis, somnolence, prominence of the pulmonary artery in the Roentgen ray and right ventricular preponderance in the electrocardiogram. This picture is not unlike the syndrome of chronic cyanosis, erythremia and enlarged spleen known as polycythemia vera or Osler-Vaquez disease, under which heading it has undoubtedly been described, as pointed out by Barlaro.[1] Although a similar picture appears in various conditions, one group of cases shows such constant and unusual pathologic findings a differentiation seems justified, and a review of the disorder described as Ayerza's disease is presented with case reports.

Historical. Although pulmonary artery sclerosis was noted almost one hundred years ago by Andral,[2] it was not until 1891 that Romberg[3] and, in 1892, Aust[4] added sufficient clinical data to their pathologic findings to construct for us the first rough picture of the black cardiac. In 1901 Abel Ayerza, professor of clinical medicine in the National University of Buenos Aires, lectured on the syndrome of chronic cyanosis, dyspnea, erythremia and pulmonary sclerosis, and, as he was the first to recognize it, it has been given his name. In 1908 Posselt[5] discussed the clinical diagnosis of pulmonary artery sclerosis, recognizing the value of the Roentgen ray findings and of the electrocardiogram. As far as is known the term, "Ayerza's disease," first appeared in the literature in 1909 in a doctoral thesis by Marty.[6] In 1910 Giroux[7] wrote an exhaustive thesis on pulmonary artery sclerosis and collected 66 cases, nearly all secondary to other pathologic changes. In 1912 Arrillaga[8] gave a fine description of the syndrome, and reported 11 cases. Warthin[9] reviewed the condition in 1917, collecting and reporting all cases of Ayerza's disease to date, and published a detailed report of a case in 1919.[10] Recently Luis Ayerza[11,12] has discussed the nomenclature and bibliography. Osler's *Textbook* mentions the condition under erythremia.

Etiology. The disease affects males slightly more often than females, there being 15 men in 27 cases collected from the literature.

It occurs from early adult life up to the sixth decade, the youngest known patient having been twelve years of age (Roger's[13] case of a married Hindu girl) and the oldest fifty-five years of age. It has been observed in Europe, South America, the United States and India. Apparently a definite preliminary stage is usually necessary for the final development of the syndrome of the black cardiac, and this is a chronic inflammation of the bronchi from one to twenty-five years' duration, which in the beginning differs in no way from the chronic bronchitis and emphysema so commonly seen. Some time following the increase in tension in the pulmonary arteries a sclerosis of the vessel walls develops and then the symptoms which Professor Ayerza so carefully described begin to appear, converting a frequent, well-recognized disorder into an unusual and little-described one. The cause of the arteriosclerosis is usually or possibly always syphilitic, most cases showing a positive blood Wassermann or other evidences of syphilis. Alcohol, malaria, smallpox and tuberculosis have been mentioned as causes, but their relation to the condition has never been proved. Certainly the etiologic factors are variable and may be more exactly determined by further study.

Pathology. Necropsies have been performed in 28 cases. These disclose certain lesions in the heart, lungs and pulmonary arteries which are sufficiently constant to be diagnostic. As the patients usually die from cardiac failure, the organs in general show chronic passive congestion, and the liver and spleen are enlarged. Changes indicative of lues may be found elsewhere than in the pulmonary arteries. The heart is greatly enlarged with dilated chambers and marked muscular hypertrophy of the right ventricle; the left ventricle by comparison seems more of an appendage than an important part of the organ, and the valves are normal. The myocardium may show some fibrosis, fatty infiltration or brown atrophy. The lungs show the effect of chronic bronchitis and emphysema plus congestion, and not infrequently the presence of bronchopneumonia. A chronic syphilitic bronchopneumonia with miliary gumma has been described in 1 case.[14] The lungs are voluminous, dark red, firm and wet, and areas of atelectasis alternate with areas of emphysema. The bloodvessels are distended. Microscopically, brown induration, resulting from long-standing congestion, is marked. The bronchi are dilated and show desquamated epithelium, atrophic muscle fibers, round-cell infiltration and increase of connective tissue, which may undergo hyalin degeneration. In one area the alveoli are dilated and fused with marked desquamation of epithelium; in another they are compressed and atrophic, the walls thickened by connective tissue and hyalin changes are present. The dilatation and sclerosis of the pulmonary arteries are the striking and unusual features of the necropsy findings. The larger arteries are markedly dilated and show sclerotic changes of the

inner media and of the intima; the smaller ones show extreme endarteritis of the same layers, while thrombi are frequent. Microscopically, the cell proliferation of the media and intima almost occludes the lumen in the smaller arteries, and the elastic fibers lose their normal parallelism and become interlaced. Some round-cell infiltration around the vasa vasorum is constant, and thick hyalin vessel walls may be seen.

Symptoms. In the early stage these patients cough and expectorate and breathe with difficulty just as in chronic bronchitis, emphysema and asthma; then cyanosis is noted and further symptoms slowly appear, which are unusual in these pulmonary disorders, and when all are manifest the black cardiac merits his name. Escudero[15] divides the course into the "periode bronchique" and "periode cardiaque." In Roger's cases,[13] which he believes are all syphilitic, the early stage was infrequent and the rapid course is probably due to the susceptibility of the Hindus to the infection.

Cough is usually of long standing; it may precede the cardiac stage by thirty years and has always been noted as present. It attacks the patient in spells and is increasingly productive. The *sputum* is mucopurulent and in time becomes abundant and is frequently streaked with blood. *Dyspnea* is a constant early symptom, often the first complaint, and increases insidiously as in other forms of cardiovascular disease. Effort dyspnea grows into constant dyspnea present even when sleeping. The respirations may be as high as 30 per minute. *Cyanosis* has an insidious onset and is the forerunner of more disturbing symptoms. At first it may be intermittent, occurring when the patient has an attack of bronchitis, but later is constantly progressive with striking increases in intensity when the patient coughs, struggles for breath, vomits, or during attacks of substernal pain. During cardiac decompensation it is so intense as to suggest the term black cardiac. The blue-violet color affects the whole body, but is most marked in the conjunctiva, the ears, the lips, the nose and beneath the nails of the fingers and toes. The buccal mucosa and throat are dusky red and the tongue is the color of "lie de vin." The drumstick fingers and toes described by the Spanish and French writers I found noted as present in only 1 case report of those which were available. *Hemoptysis* occurs due to increased tension and sclerosis in the small pulmonary arteries, and the pulmonary hemorrhage may cause the patient to cough up a large amount of blood. *Somnolence* is a pronounced and characteristic feature of the black cardiacs, and these "sleepy heads" literally live to sleep, fall asleep while eating and die in their sleep. However, insomnia due to extreme dyspnea is a frequent incident in acute cardiac decompensation. *Vertigo* is uncommon, but may be one of the chief symptoms and fatigue and palpitation are frequent early complaints. *Angina hypercyanotica* is brought on by effort. It consists in a

sense of severe oppression at the base of the heart, radiating out into the lungs, accompanied by an increase in cyanosis and quite comparable to the pain of luetic aortitis, although less intense. Gastrointestinal symptoms are common late manifestations as in other cardiacs, and gaseous distention, epigastric pain and vomiting occur frequently. Headaches may be severe and wake the patient from his customary sleep. *Edema* is usually a late occurrence, but it may first appear years before death. It was noted as present in 13 out of 16 cases and absent in 3. Arrillaga[16] has emphasized nine symptoms—"cyanosis, polyglobulia, clubbed fingers, dyspnea, hemoptysis, headache, sleep, hypercyanotic angina, angina pectoris."

Physical Examination. The patient appears cyanotic, the fingers and toes may be clubbed and edema of the extremities is common. The chest is emphysematous, fixed in the permanent position of inspiration, with retracted apices, sternum and lower intercostal spaces. The lungs are hyperresonant. The areas of hepatic and cardiac dullness are diminished. Fremitus is normal or diminished; inspiration is harsh; expiration prolonged and difficult. Sonorous and sibilant rhonchi are heard to a varying degree. The heart apex beat cannot be seen or felt, but a pulsation is present in the epigastrium. The area of cardiac dullness is often difficult to determine, due to the emphysema, but an increase in the right border of dullness is present. The sounds are distant; the pulmonary second sound is often accentuated and characteristically there are no murmurs. Usually no increase in dullness can be made out at the base of the heart. Clinically, the liver was found enlarged in 11 out of 13 cases where it is mentioned. The spleen has been found palpable but once in 10 cases where its condition is recorded. The pulse tends to be slow and of poor quality, and may be irregular; the blood pressure is not altered. When complications do not occur the temperature is subnormal. Ophthalmoscopic examination of the fundi shows venous engorgement and edema of the retina.

Laboratory Findings. The red blood corpuscle count is usually over 5,000,000 and may reach 10,000,000. This erythrocytosis is one of the cardinal features, and the number may vary considerably during the course of the disease. The white blood corpuscle count may show a relative lymphocytosis. The blood Wassermann was positive in 6 out of 8 cases in which it was recorded, or 75 per cent. The urine is negative except during decompensation, when albumin, casts and cells are present. The sputum rarely shows spirochetes.

Roentgen Ray and Electrocardiogram. The Roentgen ray findings are most important and their interpretation is not easy. There is a prominent shadow in the region of the pulmonary artery identified under the fluoroscopic screen as the pulmonary artery, together with an enlargement of the right heart. The heart apex may be extended outward and appear raised, giving the impression of a half boot.[17] Secondary pulmonary congestion about the hilum

regions has frequently led to mistaken Roentgen ray diagnoses, such as tuberculosis and neoplasm. The electrocardiogram shows a slight to marked right ventricular preponderance in all cases so examined.

Diagnosis. Certain outstanding features of this syndrome frequently occur in other disorders, and unless the clinical picture of chronic productive cough, dyspnea, intense cyanosis, erythrocytosis, somnolence, headache, vertigo, angina hypercyanotica and hemoptysis, described by Ayerza, is substantiated by characteristic Roentgen ray and electrocardiographic findings and evidence of syphilis, the diagnosis cannot be well assumed, and, just as in gastric syphilis, an exact diagnosis must await the pathologic report. The appearance of the patient, the somnolence, the erythremia, the retinal congestion and the unexplained cardiorespiratory embarrassment, all suggest the malady of Ayerza, but may be closely simulated by Osler-Vaquez disease,[10] or by pulmonary sclerosis, as shown by Morse.[18] In the Osler-Vaquez syndrome the heart is usually not remarkable, the spleen is much more constantly enlarged and in the Geisbock group there is hypertension. Those cases of polycythemia rubra which Parkes Weber[19] associates with congenital and with acquired heart disease present a history sufficiently typical to differentiate them.

Pulmonary sclerosis due to chronic infection or to anthracosis, or associated with asthma[20] or even emphysema, may produce a picture identical with the black cardiac of Ayerza. For example, a man, aged fifty-four years, with marked dyspnea, cyanosis, edema and extensive increase in dullness to the left in the second left intercostal space, recently died a few hours after entering the hospital. Necropsy showed a marked right heart hypertrophy with diminutive left ventricle and normal valves and greatly dilated pulmonary arteries, but no pulmonary endarteritis—all secondary to an extensive emphysema of the lungs and bronchitis. The pulmonary fibrosis of chronic infection and of anthracosis can be distinguished by the Roentgen ray, and the differentiation from asthma and emphysema would be suggested by the clinical evidences of lues or the positive blood Wassermann. Ordinary arteriosclerosis of the pulmonary artery has long been recognized as secondary to mitral heart disease, emphysema, chronic bronchitis, adhesive pleurisy, tuberculous pulmonary induration and synechia cordis, but the essential feature of Ayerza's disease is a primary sclerosis and endarteritis of the pulmonary arteries which apparently accounts for some of the more characteristic cardiac symptoms. The diagnosis of the presence of malignant disease in the thorax may be suggested by the Roentgen ray findings.

Prognosis and Treatment. The ultimate outlook is bad, but some cases carry on for years, even after they have entered the cardiac stage. Cardiac incompetency may progress rapidly to complete

decompensation and death from right heart failure, or the patient may simply sleep once too often. The treatment of the bronchitis and of cardiac failure must be symptomatic. When syphilis is proved present antisyphilitic treatment should be instigated, but its efficacy must depend on an early diagnosis.

Case Reports. CASE I.—*History.* E. R. C., aged forty-seven years, married, white, goldminer, was brought by motor from the country to the hospital. The complaint was dyspnea. One brother and one sister had died of pulmonary tuberculosis and one sister of heart disease. He had been separated from his wife for five years and there was no history of miscarriages. He had done little active mining in recent years and had not drunk heavily. He had a generalized rheumatism thirty-two years, typhoid fever fourteen years before and influenza seven years before his hospital admission. Otherwise he had been well except for a cough for a number of years until one year previous. Since then he had suffered from shortness of breath, pain in the pit of the stomach and constipation. For six months he had had more or less constant swelling of the hands and feet, and three months before he was prostrated with an attack of "kidney and liver" trouble. For three weeks he had suffered from extreme dyspnea, insomnia, cough with sticky sputum and extensive edema of the extremities, and for one week he had been confined to bed. The time of onset of cyanosis had not been noted; there was no complaint of precordial pain, vertigo or headache.

Physical Examination. The patient was large, well developed and muscular. He was somewhat confused mentally. His generalized cyanosis gave the impression of a grown-up "blue baby." His face, neck, hands and feet were the color of a ripe Damson plum, the discoloration being more intense in the ears, nose, lips and beneath the finger nails and toe nails. The cyanosis increased on coughing, vomiting and with the occurrence of chest pain. The pupils were not unusual; the conjunctivæ were bluish. The tongue and the mucous membranes of the mouth and pharynx were purplish. The teeth were in fair repair; the tonsils were small, embedded and atrophic. The veins of the neck were distended. The thorax appeared symmetrical and cylindrical, with shallow respiratory movements at the rate of 24 per minute, and apices and bases almost fixed throughout the respiratory cycle. There was pitting edema posteriorly and over the lumbosacral region. Tactile fremitus was equal on both sides and the percussion note hyperresonant except for dullness over both lung bases. The breath sounds were suppressed and harsh, expiration prolonged and rough and numerous humid râles occurred at the bases throughout the respiratory cycle. He frequently coughed up a tenacious mucopurulent sputum. No cardiac pulsations were seen or felt except diffuse feeble waves in the epigastric region. The left border of cardiac dullness in the fifth left intercostal space was 10 cm. from the midsternal line. The right border of cardiac dullness could not be ascertained, due to overlying lung tissue. The supracardiac dullness was 7 cm.; no area of absolute cardiac dullness was made out. The sounds at the apex were very distant, those at the base were barely perceptible and the aortic second sound equaled the pulmonary second sound in intensity. A blowing systolic murmur was present at the apex. The heart rate was 72 to 76 per minute and very irregular; the pulse rate, 30 to 40 at entrance, irregular and the quality poor. The systolic blood pressure was found to be 130; the diastolic could not be obtained. The abdomen showed a distention, anasarca of the wall, and no evidence of ascites. Liver dullness extended in the right nipple line from the fourth intercostal space to 7 cm. below the costal

margin, where a smooth tender lower edge was palpable. The spleen was not palpable. The genitalia were swollen and edematous. The right arm and both legs showed marked edema; the hands and feet felt cold; the fingers and toes were not clubbed; the deep reflexes of the legs were absent. Lymph glands, bones and joints were not found unusual.

Laboratory Findings. An amber, turbid acid urine with specific gravity of 1018 contained a heavy cloud of albumin a few hyalin casts and many red blood corpuscles and white blood corpuscles. The blood was very thick and dark. The hemoglobin was 92 per cent. The blood count showed 5,720,000 red cells and 20,500 white cells. The color index was 0.8. The differential white cell count was: Polymorphonuclears, 89 per cent; lymphocytes, 9 per cent; basophils, 1 per cent; transitionals, 1 per cent. The morphology of the red cells was normal. The blood Wassermann reaction was positive.

Course. His temperature dropped from normal to 96° F. rectally; the pulse varied from 30 to 70, becoming more regular; the respirations dropped to 15. He had no passage of urine or stools, but 15 cc. of urine were withdrawn by catheter. He grew extremely weak, cold and cyanotic, sleeping at half-hour intervals, and suffering at times from severe attacks of low substernal and epigastric pain well localized. The mucopurulent sputum was blood tinged. He could retain no food and vomited blood and continually demanded ice water. Despite stimulations, warmth and phlebotomy he died twenty-nine hours after admission to the hospital while apparently deep in sleep. The clinical diagnosis was chronic luetic myocarditis, cardiac decompensation, chronic passive congestion of organs.

Autopsy. The body had been embalmed. There was marked edema of the right arm, both legs and thighs, and of the genitalia. Incision disclosed a moderately thick layer of subcutaneous fat and an edematous abdominal wall. The diaphragm level was the sixth intercostal space on the left, the fifth on the right. The chest was barrel shaped; the costal cartilages not calcified; the anterior mediastinum edematous. There were a few light adhesions about the apex of the left lung, and the right pleural cavity contained about 500 cc. of embalming fluid.

The pericardium was not unusual. The heart was enlarged about one and a half times; the tricuspid orifice admitted four fingers and the mitral two. The right auricle was greatly dilated with three masses of thrombi firmly adherent to the walls. One part filled the auricular appendage and the two others attached to the right of the appendage measured 2 cm. in diameter. The right ventricle was tremendously dilated with hypertrophied walls measuring 5 mm. in thickness. The left auricle and ventricle were moderately dilated with walls of normal thickness. The valves of the heart were normal except for relative insufficiency of the tricuspid. The base of the aorta showed many atheromatous spots and much scarring. The coronary arteries were normal.

The lungs were large and emphysematous. The bronchi were greatly congested and contained dark brownish mucus. There was a scar at the left apex and a grayish yellow caseous nodule 1 cm. in diameter in the right upper lobe. The pulmonary arteries were dilated and contained a number of atheromatous areas. The right branch of the pulmonary artery measured 3 cm. in diameter and was completely plugged up with thrombus. One branch was occluded for a distance of 6 cm., while there were other thrombi in the smaller branches. There was a large thrombus at the bifurcation of the left pulmonary artery and other thrombi further down in the descending branches were firmly adherent to the walls. The lung tissue was edematous and deep brownish red in color. There were no areas of consolidation.

The spleen was somewhat enlarged, the capsule thickened and on section showed firm pulp and marked passive congestion. The adrenal glands

were normal. Both kidneys were slightly above normal size, with capsules stripping readily, leaving a smooth surface. Cut surface showed marked passive congestion of the pyramids and opacity of the cortex. The renal arteries were dilated with thickened walls. The bladder was retracted and empty, with normal mucous membrane. The prostate was normal; the rectal mucosa was markedly congested.

The duodenum contained much bile-stained mucus. The mucous membrane of the stomach was covered by a thick coating of dark mucus; the mucosa was greatly congested and contained a number of irregular hemorrhagic erosions and some petechial hemorrhages. The intestine was not opened. The gall bladder was adherent to the transverse colon and contained dark, thick viscid bile. The liver was small, the capsule thickened and cut surface exhibited a marked cyanotic atrophy. The pancreas was normal. The thoracic and abdominal aorta showed many atheromatous plaques, and thickened walls with scarring and longitudinal wrinkling. The inferior vena cava was slightly dilated.

Histologic Examination. The heart showed diffuse scarring of the right ventricle with very little of the left, intense fatty degeneration and moderate arteriosclerosis. A section through the right auricular thrombus showed organization, beginning calcification and large collections of phagocytes containing fat in the fibrous tissue. There were marked irregular fibrous thickenings of the aortic intima, with large areas of necrosis and calcification. Scarring also occurred in the media about the vasa vasorum, accompanied by round-cell infiltration. Fibrous thickening of the adventia with round-cell infiltration was present. Sections of the lungs disclosed bronchi stripped of epithelium, but otherwise not unusual. In most places the alveoli were dilated with thin walls and many were ruptured and confluent. The fibrous tissue in the walls was slightly increased. Some areas showed atelectasis with increase of connective tissue and much cellular débris. The alveoli contained great numbers of heart failure cells, red blood corpuscles and desquamated epithelial cells. Only moderate carbon pigmentation was noted. The large branches of the pulmonary arteries showed sclerosis (Fig. 1) and adherent thrombi, with striking round-cell infiltration of the vasa vasorum of the adventitia (Figs. 2 and 3). There was a loss of elastic tissue in the media, and the fibers were interlacing and presented a frayed-out appearance at the ends. The smaller branches showed extensive proliferation of the intima which almost occluded the lumen in many, the inner media being much increased also (Figs. 4 and 5). In some the endarteritis completely occluded the vessels. Sections stained by Levaditi's method failed to disclose any Treponema pallidum. Tubercles containing giant cells and tubercle bacilli were demonstrated in the caseous nodule from the right lung. The kidneys showed cortical scars with diffuse fibrosis of many of the glomeruli, which were large and congested. The tubular epithelium was swollen, granular and had undergone fatty degeneration. The arteries were arteriosclerotic. The liver showed marked signs of congestion, with central hepatic cell atrophy and phagocytic cell infiltration. There was extreme congestion of the venous sinuses of the spleen and thickening of the smaller arteries with hyalin degeneration. The adrenals showed a diffuse fibrosis with excess of lipoid of the cortex. The pancreas was poorly preserved and showed some granular swelling of the epithelial cells. There were small adenomatous areas in the prostate with dilated glands and periglandular round-cell infiltration.

Anatomic Diagnosis. Emphysema of the lungs; arteriosclerosis, local, of the pulmonary arteries with dilatation and hypertrophy of the right ventricle (Ayerza's disease); bilateral thrombosis of the pulmonary arteries; thrombosis of the heart, auricular appendage and right auricle; arteriosclerosis, general; tuberculosis of the lungs, apical, healed and recent; focal syphilis of the aorta, probably; hypertrophy of the prostate.

Comment. This man's history, physical examination, erythrocytosis and positive blood Wassermann should have suggested the clinical diagnosis of Ayerza's disease, but the pathologic findings are so typical they establish the diagnosis. It is to be regretted that his critical condition did not permit a complete clinical investigation.

Dr. Ernest Hall, of the department of pathology, performed the autopsy, and I am indebted to him for the microphotographs.

CASE II.—*History.* Mrs. E. B., aged forty years, separated from husband, American, saleswoman, was sent into the hospital clinic ward on January 24, 1924, by Dr. Leo Eloesser. Her chief complaint was difficulty of breathing on exertion. Her father had died of heart failure and her mother and her first husband of tuberculosis. Her second husband was living and well. She had had only one child, a son, aged twenty-three years. She had measles and mumps in childhood and appendectomy for an acute appendicitis eleven years ago. Eight years ago she had pneumonia followed by pleurisy and spent the subsequent year in Arizona, as pulmonary tuberculosis was suspected. No sputums positive for tubercle bacilli were reported. At first she coughed up some blood, but later gained weight and did very well. She is subject to colds and one year ago had influenza. Her menstrual periods had been irregular for three months. She denied veneral infection. She dates her present illness back five years, when she noted dyspnea on exertion. This has progressed steadily until now she can hardly move without extreme shortness of breath and this condition has been accompanied by an intense blue color of her hands and face. She is more comfortable lying flat in bed and is awakened at night feeling suffocated and gasps for breath. She coughed up blood several times one year ago, and also suffered with attacks of epigastric pain and gastric distress. She had not suffered from headache, somnolence or chest pain.

Physical Examination. She was rather fat and well nourished and showed marked cyanosis of the face, lips, neck, hands and feet on the slightest exertion. The pupils were unequal and slightly irregular, but reacted promptly to light. The tonsils were large and infected. The chest was symmetrical and expansion full and equal. The lungs were resonant to percussion, the fremitus equally and well transmitted, the breath sounds not unusual and an occasional course râle was heard. The heart apex impulse was not seen nor felt, and the area of cardiac dullness was increased both to the left and to the right. The heart sounds were clear and regular, free from murmurs, and the pulmonary second sound was markedly accentuated. The abdomen was obese. There was an old right lower quadrant scar. The liver and spleen were not palpable. The extremities showed no edema, there was no clubbing of the fingers or toes and the knee jerks were active and equal. The blood pressure was 180 systolic and 125 diastolic. The uterus was one and a half times the normal size and quite hard.

Laboratory Findings. Nothing abnormal was found on urinalysis. The blood count was 5,101,000 red blood cells; 90 per cent hemoglobin; 14,300 white blood cells, 61 per cent of which were polymorphonuclear leukocytes, 35 per cent lymphocytes and 4 per cent large mononuclear cells. The blood film appeared normal. The sputum was thick and mucoid and showed no acid-fast bacilli. The blood Wassermann was negative. Fractional gastric analysis revealed a low total acidity and no free hydrochloric acid. The phenolsulphonephthalein renal function test gave 40 per cent dye excretion after two hours.

FIG. 1.—Large branch of a pulmonary artery showing extensive sclerosis. Case I.

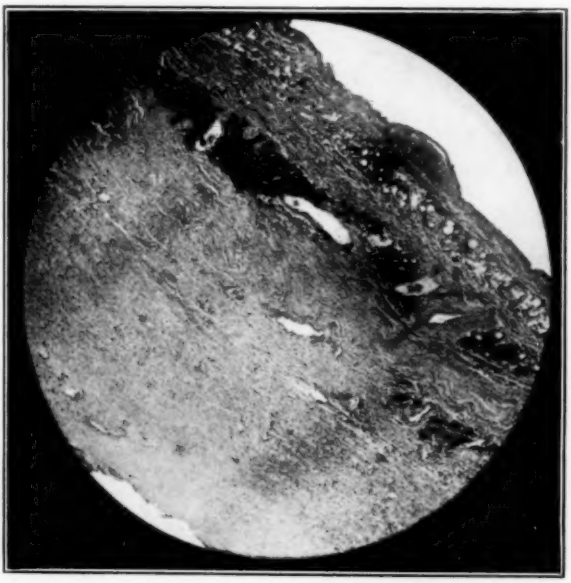

FIG. 2.—Round-cell infiltration of the vasa vasorum of the adventitia of the pulmonary artery. Low-power. Case I.

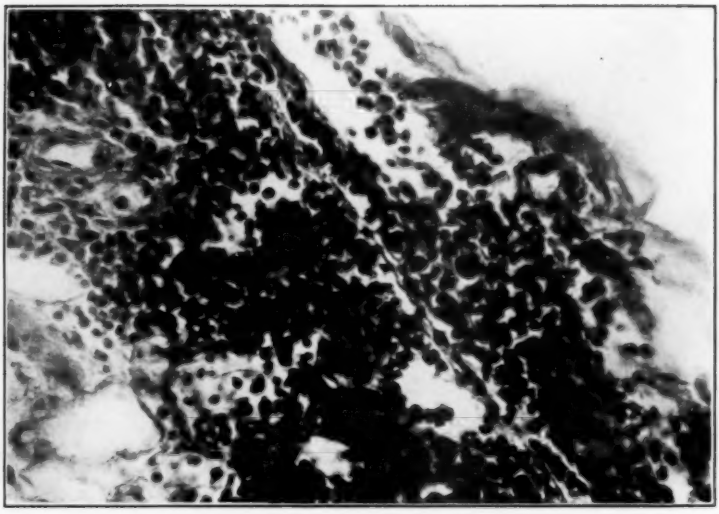

FIG. 3.—Same as Fig. 2. High-power.

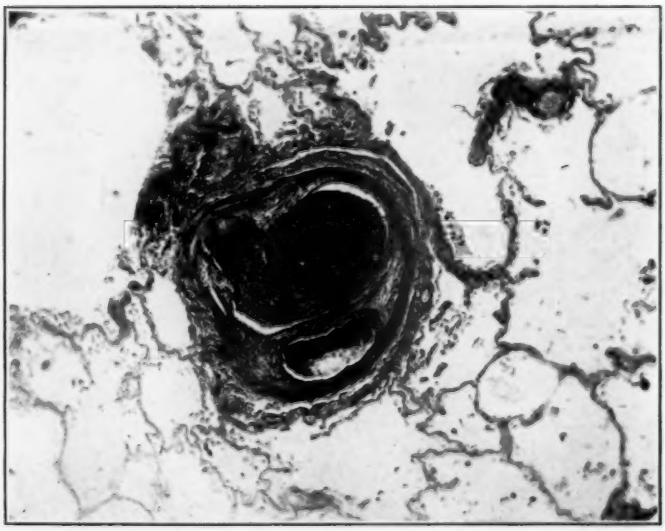

FIG. 4.—Marked endarteritis of one of the smaller pulmonary arteries. Case I.

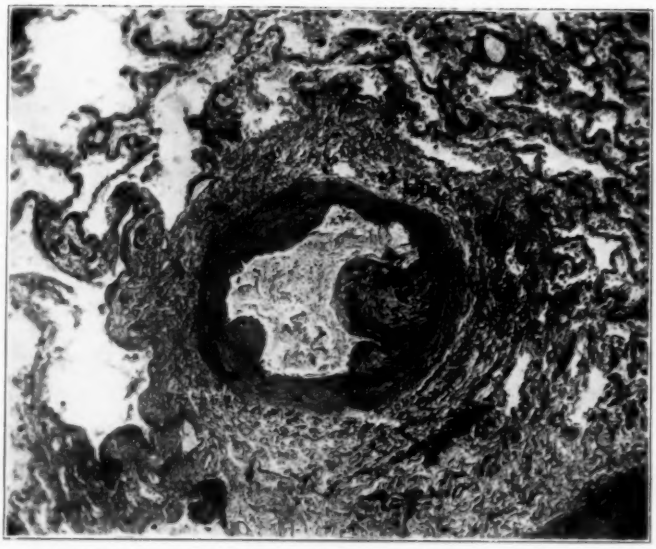

FIG. 5.—Proliferation of the intima and inner media of a small pulmonary artery. Case I.

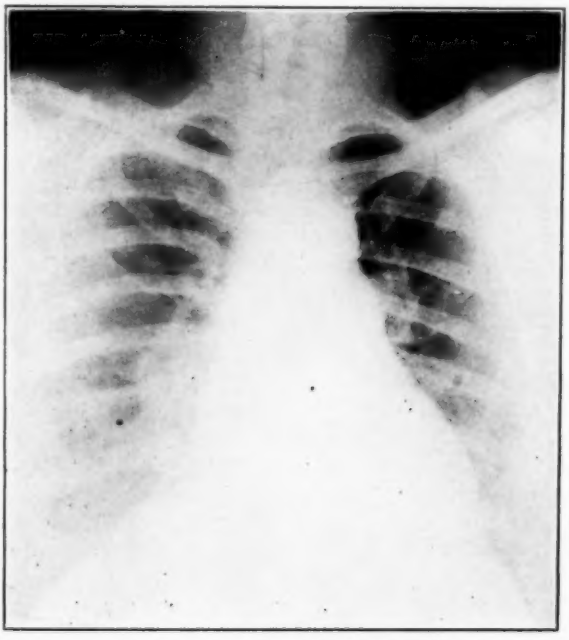

FIG. 6.—Roentgen ray of chest in Case II showing prominence of the pulmonary artery, enlarged heart and lung root congestion.

The Roentgen ray (Fig. 6) report of the chest noted a nodular density in the right lung root suggesting tumor, a heart shadow considerably increased in area—its shape not indicating which chambers might be enlarged—a definite overprominence of the arch of the pulmonary artery and diffuse grayishness of the lung fields interpreted as passive congestion. The gastrointestinal series showed pylorospasm, spastic gastric antrum and poorly outlined duodenal cap (suggesting gall bladder disease).

The electrocardiogram showed right ventricular preponderance with the *T* wave negative in Leads II and III. The vital capacity was 71 per cent.

Course. She remained in the hospital but two days, and had intense cyanosis and dyspnea when moving about. The temperature varied from 96.8° to 98° F., the pulse between 72 and 87, and the respirations between 18 and 21. The urine output was good and the bowels were open. The late Dr. A. W. Hewlett made the diagnosis of sclerosis of the pulmonary artery. Unfortunately the patient cannot now be traced.

Comment. This patient had an eight years' history of chest trouble with cough and hemoptysis, dyspnea and intense cyanosis, on exertion, and on physical examination the lungs were essentially negative, and the heart was enlarged to the left and to the right and without murmurs. The apex beat could not be seen or felt and the pulmonary second sound was unusually accentuated. The red blood cell count was just over 5,000,000 and the temperature was persistently subnormal. In the absence of any other evidence to account for the patient's condition, and despite a negative blood Wassermann, the right ventricular preponderance in the electrocardiogram and the prominence of the pulmonary artery in the Roentgen ray suggest the diagnosis of Ayerza's disease in a not far advanced stage.

Collected Case Reports. A review of the literature on pulmonary artery sclerosis reveals 40 cases which may be classed as Ayerza's disease, although from the data presented it has been difficult to accurately interpret the reported findings, especially when autopsies have not been performed. I found 28 records including pathologic findings characteristic of Ayerza's disease in which there was nothing else present to account for the right heart hypertrophy and the arteriosclerosis of the pulmonary vessels and, while many of these showed evidences of syphilis, in others the descriptions were so meager that no just conclusions could be drawn. As the condition has been so little and so inadequately described, I have divided the total number of cases into more or less arbitrary groups, depending on the completeness of the case reports.

Nearly all the earlier reports were chiefly pathologic ones, with few or no clinical findings given, and they were studied when the modern means of laboratory diagnosis did not exist. Such cases were described by Klob,[21] Crudeli,[22] Volfram,[23] Laache,[24] Qwiatkowsky,[25] Kitamura,[26] Scheel,[27] Rössle,[28] Rogers,[13] and Sanders.[29] The majority of the cases fall into a group incompletely studied from the point of view of our present standards of diagnosis, but

autopsy findings are added to complete the picture. Blood counts and blood Wassermanns were not ordinarily included. Such are the reports of Romberg,[3] Aust,[4] Mönckeberg,[30] Rogers,[13] Arrillaga[8] and Hart.[31] In addition to the second case presented in this article, Mayer[17] (2 cases), Arrillaga[32] and Barlaro[1] have given complete clinical descriptions of cases which have not come to necropsy. The 2 cases described by Lucas,[33] in his very extensive discussion of erythremia, do not appear to be in the Ayerza's disease group. Warthin,[10] and Elizalde and Arrillaga,[14] and recently a clinical pathologic conference at Ann Arbor,[34] have given fine clinical and pathologic reports.

Summary. (1) A brief review of the clinical, laboratory and pathologic features of the syndrome known as Ayerza's disease is presented, and it is suggested that this term be restricted to those cases of pulmonary artery sclerosis and resulting right heart hypertrophy which are due to syphilis.

2. It has been pointed out that the clinical picture of the black cardiac can develop in a variety of conditions, and there may be sufficient evidence to justify the clinical diagnosis of Ayerza's disease, but one must await a final word from the pathologist.

3. Two case reports are presented. In the first the diagnosis is definite and the pathologic record complete. The second is not definite, but presents the evidence on which a presumptive clinical diagnosis may be made.

4. A survey of the literature includes all known cases and emphasizes the rarity of the malady.

5. A practically complete bibliography of Ayerza's disease is appended.

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NEWER HEMATOLOGIC ASPECTS OF THE NEUTROPHILS IN INFECTIONS.*

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The enormous progress of hematology during the past half century, may be directly attributed to Ehrlich's epoch-making discovery of suitable blood stains. By this discovery hematology as such was enabled to assume its rôle as one of the exact sciences. Although before him, van Leeuwenhoek had already discovered the erythrocytes, Hewson the leukocytes, Addison and Biermer pernicious anemia, and Virchow the leukemias, it was the discovery of good stains and staining methods that ensured the accurate study of the morphology of the blood cells. By his staining methods Ehrlich was able to subdivide the leukocytes into their three respective groups—the polymorphonuclear leukocyte, or granulocyte, the lymphocyte and the large mononuclear cells. By the different staining of the granules he was further able to subdivide the granulocytes into neutrophilic, basophilic and eosinophilic.

The next great contribution in the study of the morphology of the leukocytes came with the publications of Arneth. In 1904–1905, while working at the Leube Clinic, he made the following observations on the changes in the nuclear structure of the neutrophils during infections. Whereas, normally the nuclei of the neutrophils contain from two to five segments, the three and four lobe type predominating, in infections he found an increase in the number of cells containing one and two segments with a concomitant decrease in those of the three to five segmented variety. He also found that this change was fairly constant, varying with the severity of the infection. Thus, as the infection grew worse, the number of immature cells, or those neutrophils with unsegmented nuclei, increased; with recovery and convalescence the immature forms

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lessened in number with a reversion to the two to five segmented variety. An increase of the nonsegmented and the two segmented forms he called a "Linksverschiebung," or shift to the left, and an increase of the ripe forms a "Rechtsverschiebung." He explained the appearance of these immature forms in the blood stream during infection by his "Ersatz und Verbrauch" theory. We know that normally there is a leukocytic regeneration and degeneration going on constantly in the body. By this double physiologic phenomenon there is maintained in the blood circulation a constant normal for each type of cells. We also have found that, varying with the nature of the infection, there is either a leukocytosis or a leukopenia. This increase or decrease of the white-cell elements is, contrary to previous opinions,[15] not due to any positive or negative chemotaxis that the organisms or the toxins that the organisms may be exerting on the individual leukocyte. It is due to a stimulation or inhibition of the bone marrow by the bacterial toxin. Arneth claims that with the increased destruction going on in infections there is an increased demand on the bone marrow. The bone marrow having sent out all of its mature forms is unable to supply the demand for fully developed cells, has to send forth cells as rapidly as it can make them and hence the presence of the large number of young granulocytes. Arneth in his study of the leukocytic morphology has also subdivided the lymphocytes and monocytes. After employing his complete classification (81 subdivisions), however,[14] I have been unable to find any definite value in the lymphocytic and monocytic subclasses.

The appearance of Arneth's careful observations on the morphology of the leukocyte aroused immediate interest both in the United States and abroad. Numerous authors, the majority of whom were working on tuberculous material, took this work up and began to employ it quite extensively. Nevertheless, just as his scheme aroused immediate interest, it just as rapidly fell into disrepute. A careful perusal of the literature of those men who had employed Arneth's classification extensively, reveals that all of these authors found it to be of definite value in prognosis of tuberculosis and also found it to be a guide in its treatment. Those, who at the start were under the impression that by means of this classification, they would be able to diagnose the amount of lung involvement soon found themselves disappointed. Those who learned its limitations, were quite positive of its value and never discarded its use. There is one thought voiced by all of those who have used this classification, and that is the inability to understand why this method never gained ground.

Why has this procedure never become a popular one? Judging from those who have employed it, there can be no doubt that as a laboratory procedure it is of definite value and has definite information to offer to the clinic. Anyone who has employed Arneth's

original classification can easily answer for its nonpopularity. After some experience with it I[14] found that to do a complete Arneth count took forty-five minutes. To one just beginning to use it the time necessary would be much increased. To do a differential and only using the subdivision of the neutrophils took twenty minutes. Aside from the extravagant expenditure necessary, I also found that it was often extremely difficult to differentiate definitely between the shape and number of the nuclear segments. If the blood smear is not thin and even, it is absolutely impossible. Thus the Arneth classification is more or less technically difficult, and to be done accurately consumes more time than the physician generally allots to a blood examination.

Among the men who applied and studied Arneth's scheme thoroughly, Schilling[13] was able by certain modifications to make it less timestaking and just as valuable. He found that the separate subgroups, such as the two, three, four or five segmented forms and their subclasses as to nuclear form were superfluous, and that they could all be included under one heading, that of the segmented forms. The nonsegmented forms, however, he subdivided further into the metamyelocyte of Pappenheim, the jungkernige and the stabkernige, the staff or rod form. Furthermore, instead of subdividing 100 picked neutrophils into the numerous Arneth subclasses (or the modified five classes used by the English writing authors), he incorporated his neutrophilic grouping into the differential. Thus only 100 cells need be counted and, whereas the original count took twenty minutes, this one only takes five minutes. Pons and Krumbhaar,[17] recently reporting a case of infected bleeding adenocarcinoma of the breast, call our attention to the presence of an extremely high percentage of immature neutrophils (120,000 leukocytes; 82 to 84 per cent. young granulocytes). They also advocate the employment of a further simplification of Schilling's modified Arneth method, whereby the jungkernige and stabkernige are combined as young forms, thus adding only two extra groups to the ordinary differential count, of which two the metamyelocyte seldom occurs in normal blood.

Arneth's original procedure did not stand the acid test. It was the desire to determine definitely whether or not the Schilling modified Arneth classification was superior to the method now[15, 16] universally used, that caused me to install this method in our hematologic laboratory. Since its inception I have been able to gather information from about 1000 consecutive blood examinations done at the hospital. In all of these examinations the morphology of the leukocytes was minutely studied. In the following tables and charts I have taken a number of cases to demonstrate our findings. In the tables B. stands for basophils, E. for eosinophils, M. for myelocytes, Mt. for metamyelocytes, St. for staff or rod forms, S. for segmented forms, Ly. for lymphocytes and Mo. for monocytes.

In the charts the heavy line represents the percentage of immature cells (metamyelocytes plus staff forms) and the broken line the temperature.

TABLE I.—MASTOIDITIS, SINUS THROMBOSIS.

S. A., female, aged thirteen years.

Date.	R.B.C.	Hb.	W.B.C.	B.	E.	M.	Mt.	St.	S.	Ly.	Mo.	
July 12	4,800,000	60	14,400	..	..	..	..	26	69	4	1	
	4,980,000	63	6,500	..	..	..	..	17	61	20	2	
13	4,720,000	65	12,700	..	1	..	..	20	58	19	2	Ligation of jugular vein and occlusion of lateral sinus.
14	4,560,000	65	10,100	..	..	..	2	34	39	19	7	
15	4,440,000	73	11,000	..	..	..	1	25	63	17		
16	3,680,000	60	16,000	..	..	..	1	19	52	28	..	Revision of mastoid.
18	4,480,000	73	9,500	..	..	..	1	14	50	25	10	
19	4,240,000	70	8,500	..	2	..	..	4	36	57	1	
20	5,040,000	80	16,000	..	1	..	2	8	70	27	4	
22	4,840,000	78	8,700	..	..	..	..	9	50	38	1	
23	5,280,000	80	7,500	..	..	..	..	7	45	44	4	
26	5,840,000	82	16,000	..	..	..	..	3	41	51	8	
28	...	..	...	..	1	..	..	3	31	60	5	
30	4,320,000	75	9,300	..	..	..	..	6	42	46	6	
Aug. 5	4,240,000	72	8,500	..	..	..	..	1	39	59	1	
9	4,080,000	75	7,000	..	4	..	..	2	34	59	1	

Table I shows sustained high level of immature neutrophils even after ligation of the jugular and occlusion of the lateral sinus. Return to normalcy evident immediately after revision of mastoid.

Case Reports. CASE I.—S. A., female, aged thirteen years, entered the otolaryngologic service on July 12, 1924, with the previous history of having had an operation on her right mastoid a few months prior. She had been home only a few days when she developed fever and entered the hospital with a temperature about 103.5° F. and pain along the course of the right jugular vein. Table I shows the course of the disease as seen by the bone marrow reaction. Ligation of the right jugular vein, done on July 13, apparently temporarily increased the bone marrow irritation. After the reopening of the mastoid wound the number of immature cells, or staff forms, decreased and returned to normal. The high lymphocyte count indicates that the entire process is the healing stage. Chart I shows very clearly the rise of the staff forms at the height of the infection and the gradual drop to normal with the termination of the disease process. The patient left the hospital cured.

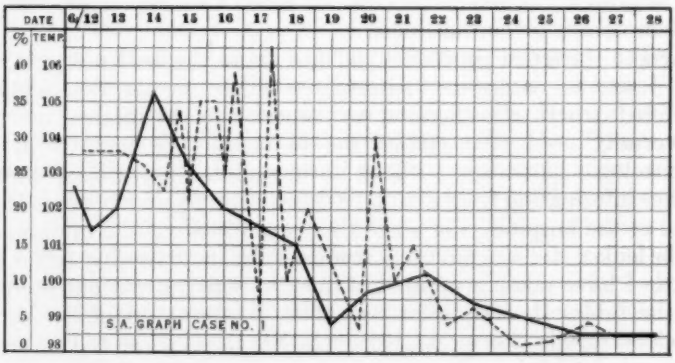

CHART 1

CASE II.—A. B., female, aged five and a half years, entered the pediatric service complaining of marked tenderness and pain in the right lower extremity, especially about the hip, and high temperature. In spite of the definite infectious count, the surgeon called in, considering the case to be one of rheumatic arthritis, advised rest in an extension splint. As Table II well shows, the number of staff forms remained high until the right hip was incised and a large amount of pus evacuated. After a slight reactionary rise the number of immature cells gradually dropped to normal. The patient at present has some degree of ankylosis.

TABLE II.—INFECTIOUS ARTHRITIS.

A. B., female, aged five and a half years.

Date.	R. B. C.	Hb.	W.B.C.	B.	E.	M.	Mt.	St.	S.	Ly.	Mo.	
July 19	4,720,000	70	23,300	..	..	..	..	24	67	9		
20	4,800,000	65	18,600	..	..	..	..	29	55	16		
23	...	..	25,600	..	..	..	..	28	57	15	..	Deg. of neutrophils.
26	4,000,000	65	38,200	..	..	..	..	17	64	11	8	
27	4,000,000	63	33,400	..	1	..	2	30	45	20	2	
28	...	..	...	..	..	..	2	25	60	11	2	
30	...	..	...	..	6	..	..	21	49	24		
31	...	..	...	..	1	..	1	22	46	22	8	
Aug. 3	3,280,000	55	17,200	..	..	..	..	13	56	31	..	Incision and drainage of hip.
5	2,900,000	50	13,400	..	..	..	6	5	68	21		
9	...	..	...	..	1	..	..	17	58	18		
10	2,480,000	50	17,000	..	1	..	..	15	50	30	4	
16	...	..	...	..	5	..	2	4	62	26	1	
23	3,120,000	60	19,500	..	..	..	..	4	69	26	1	Purulent glands incised.
Sept. 6	...	..	...	..	1	..	..	2	63	31	3	

Table II shows course of staff cells in a protracted case of infectious arthritis. Incision of purulent foci led rapidly to a normal blood count.

CASE III.—W. I., male, aged seventeen years, entered the hospital on the fifth day of his illness. Complaints and physical examination were those of a frank lobar pneumonia. Table III shows the sharp rise of the immature cells as the crisis approached and the decisive drop in a few days of the differential to normal. Chart 3 also shows the rise and rapid fall of the staff forms of this case. The patient is convalescing nicely.

TABLE III.—LOBAR PNEUMONIA.

W. L., male, aged seventeen years.

Date.	R. B. C.	Hb.	W.B.C.	B.	E.	M.	Mt.	St.	S.	Ly.	Mo.
Sept. 2	3,540,000	60	15,000	..	..	..	2	27	65	6	
4	...	..	...	..	..	..	3	25	55	22	
5	...	..	...	..	..	..	3	34	54	8	1
6	...	..	...	..	..	2	4	44	45	5	
7	...	..	...	..	..	..	..	18	74	8	
8	3,880,000	70	26,000	..	..	..	4	17	74	5	4
10	...	..	...	..	..	..	1	9	81	9	
12	...	..	15,200	..	..	..	1	7	78	14	
13	...	..	8,000	..	..	..	1	3	87	9	
14	...	..	9,300	..	..	..	..	2	75	23	

Table III shows the gradual rise in the level of the young neutrophils until the time of the crisis and then the sharp drop to normal.

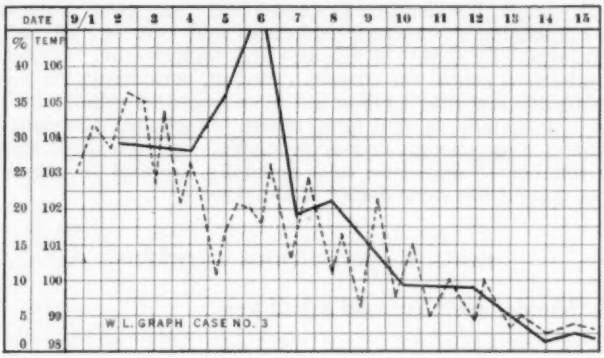

CHART 3

CASE IV.—A. W., male, aged sixty years, entered the hospital with complaints of right-sided pain in the chest, chills, fever and cough. Physical findings were those of a bilateral bronchopneumonia. The patient developed tympanites and retention of urine during the first week in the hospital. With the clearing up of these complications the patient began to look somewhat clinically improved. Blood examinations during the first half of his illness were done without the new classification. Examination of the blood counts done during the latter half show that in spite of the apparent clinical improvement the differential count was not changed for the better. It was while I was examining the smear taken on July 10 that I found that almost 50 per cent of the cells were staff forms. Upon calling up the ward to order that another smear be taken, I was informed that the patient had died. Autopsy revealed many small abscesses in the lungs. In this case, while the clinician argued for a prolonged illness and eventual recovery, the laboratory could only give a bad prognosis. Chart 4 shows the course and its ultimate outcome days before it was suspected by the temperature or clinical picture.

TABLE IV.—BRONCHOPNEUMONIA, LUNG ABSCESSES.

A. W., male, aged sixty years; died.

Date.	R. B. C.	Hb.	W.B.C.	B.	E.	M.	Mt.	St.	S.	Ly.	Mo.
June 7	4,100,000	75	14,300	..	..	..	..	..	90	9	1
10	4,300,000	75	20,200	..	..	..	..	..	86	11	3
11	4,500,000	75	17,500	..	1	..	..	..	86	11	2
13	...	..	20,000	..	..	..	..	..	91	8	1
17	...	..	18,000	..	..	..	..	..	89	8	3
28	...	..	18,500	..	..	..	2	24	54	17	9
29	...	..	15,800	..	..	..	3	23	51	14	9
July 1	...	..	...	..	..	..	3	16	54	24	2
3	...	..	17,000	..	..	..	3	15	63	15	4
6	...	..	...	..	..	..	5	28	48	18	1
7	...	..	...	..	..	..	2	29	43	21	5
8	...	..	...	..	..	..	5	30	39	21	5
9	...	..	13,400	..	..	..	3	33	46	16	2
10	...	..	...	..	..	..	2	42	41	14	1

Table IV shows marked high level of the metamyelocytes and staffs which rose to its highest peak before death. (The first few counts were done using the old method.)

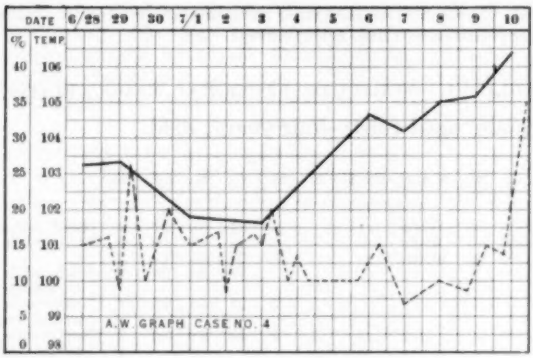

CHART 4

CASE V.—R. G., female, aged twelve years, had been in the hospital previous to present admission as a case of chronic rheumatic endocarditis. She entered the hospital on August 2, complaining of chills, fever, malaise, headache and generalized pain. The blood culture on frequent occasions showed Staphylococcus albus. During her entire stay in the hospital she had chills and elevation in temperature twice daily. She had three direct transfusions of 300 cc. each and intravenous injections of gentian violet. In spite of all therapeutic measures the patient died. Table V, of blood examinations, show a constant elevation of the staff forms.

TABLE V.—CHRONIC ENDOCARDITIS, SEPSIS.

R. G., female, aged thirteen years; died.

Date.	R. B. C.	Hb.	W.B.C.	B.	E.	M.	Mt.	St.	S.	Ly.	Mo.	
Aug. 3	3,200,000	60	22,400	..	..	..	..	7	76	15	2	Blood culture positive, staphylococcus.
5	2,960,000	55	12,000	..	..	..	..	11	79	10		
6	2,640,000	53	16,300	..	..	..	3	15	68	13	1	Direct transfusion, 300 cc. blood.
7	3,280,000	46	10,600	..	..	..	..	14	64	22		
11	3,820,000	55	19,900	..	..	..	1	13	67	19	..	Blood transfusion, 300 cc.
14	3,280,000	49	14,700	..	..	..	..	12	68	20		
16	3,480,000	45	16,500	..	..	..	..	18	71	6	5	Intravenous, gentian violet.
20	2,180,000	42	25,600	..	..	..	..	22	71	5	1	Blood transfusion, 300 cc.

Table V shows the sustained high level of the young neutrophils, in spite of direct transfusions and intravenous medication.

CASE VI.—T. H., female, aged thirty-four years, entered the hospital on March 30 and died on July 25. She was an old rheumatic cardiac who had been a patient in the hospital on two previous occasions. All laboratory data during her earlier stays were negative, including the blood cultures. She entered the hospital complaining of fever, headache and vague pains. Blood cultures at all times shows Streptococcus viridans. Table VI shows constant high level of immature forms. Neutrophils showed marked degeneration, monocytes and also showed marked hyperfunction, as evidenced by numerous large and small vacuoles. Chart

6 shows curve of the immature cells constantly high and rising with the drop in temperature as exitus approached.

TABLE VI.—SUBACUTE BACTERIAL ENDOCARDITIS.

T. H., female, aged thirty-four years; died.

Date.	R. B. C.	Hb.	W.B.C.	B.	E.	M.	Mt.	St.	S.	Ly.	Mo.	
June 27	2,900,000	55	6,800	..	..	..	..	24	51	21	4	Blood culture, Strep. vir.
29	2,960,000	45	9,400	..	..	..	..	24	60	14	2	Neutrophils degenerated.
July 1	3,500,000	60	10,400	..	..	..	3	28	48	19	2	
6	...	..	...	..	..	..	..	18	56	18	9	Neutrophils degenerated; monocytes vacuolated.
8	...	..	...	..	..	..	2	21	55	15	7	Neutrophils degenerated; monocytes vacuolated.
10	...	..	...	..	..	..	1	32	44	15	7	Neutrophils degenerated; monocytes vacuolated.
18	...	..	...	..	..	..	1	24	35	35	5	Neutrophils degenerated; monocytes vacuolated.
24	...	..	...	..	..	..	..	36	40	20	3	Neutrophils degenerated; monocytes vacuolated.

Table VI shows persistence of a high level of young neutrophils, which attained its highest level before death.

CASE VII.—J. G., male, aged fifty-six years, entered the hospital complaining of swelling, tenderness and pain of the right arm. The temperature was 103.8° F. A small incision was made, yielding some thin serous fluid; arm was not incised deeply for fear of the possibility of erysipelas. Table VII shows very nicely that the primary operation had not been successful, as the immature cells kept on mounting. With revision of the wound and evacuation of a very large pocket of pus, we find that the differential rapidly became normal.

TABLE VII.—CELLULITIS OF THE RIGHT ARM.

J. G., male, aged fifty-six years.

Date.	R. B. C.	Hb.	W.B.C.	B.	E.	M.	Mt.	St.	S.	Ly.	Mo.	
Aug. 31	3,200,000	60	5400	..	..	..	3	12	82	3	..	Incision and drainage.
Sept. 2	3,060,000	55	9400	..	..	..	3	14	75	8		
3	...	..	...	..	..	..	..	18	60	16	6	
4	...	..	...	..	..	..	..	15	61	24		
5	...	..	...	..	2	..	3	32	51	7	5	
6	...	..	...	..	..	..	..	35	53	12	..	Revision of wound.
8	...	..	...	..	1	..	2	23	52	10	12	
9	...	..	...	..	..	..	..	6	64	20		
11	...	..	...	..	1	..	1	9	70	15	4	
14	...	..	...	..	1	..	..	6	74	14	5	
15	...	..	...	..	1	..	..	3	65	30	1	

Table VII shows the course of the young neutrophils which remain above normal until the evacuation of a large pus pocket was affected. With free drainage differential dropped to normal.

CASE VIII.—M. G., female, aged four years, entered the hospital on June 18, complaining of swelling of legs, puffiness of the face and scantiness of urinary output. Urine had 4+ albumin, hyalin and granular casts and many white blood cells. The temperature was intermittent, rising daily to 106° F. and dropping to normal for a number of days and then remaining without temperature for a period. With rest in bed, restricted diet, purgation and hot packs, all evidence of edema disappeared but the intermittent temperature. With the administration of hexylresorcinol the temperature disappeared and the staff count returned to normal.

CASE IX.—R. C., female, aged four years, gave a history of sore throat and abdominal pain. She was treated on the outside for a tonsillitis. As abdominal symptoms remained, the physician sent the patient into the hospital as a surgical abdomen case. The patient was operated upon and perforated appendix with peritonitis was found. Table IX shows a

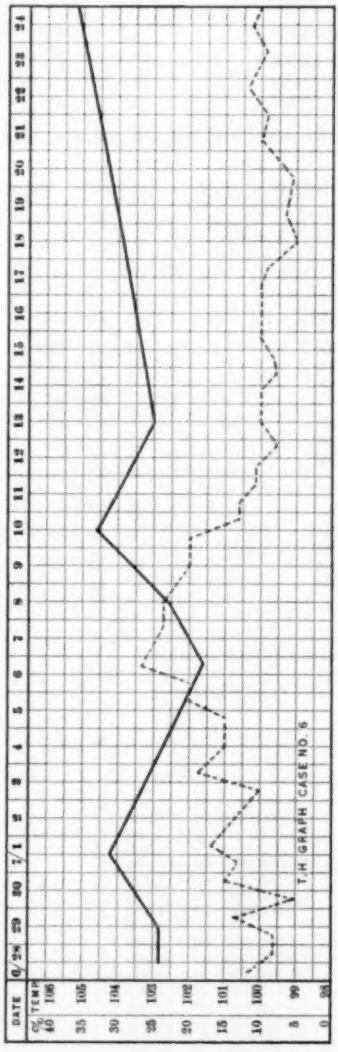

CHART 6

leukopenia, with an exceptionally severe bone marrow stimulation. Neutrophils show marked degeneration. Eleven days after operation the staff count was still high. The patient was reopened and a large residual abscess drained. Here, also, the operation acted as a temporary stimulant on the bone marrow with its resulting increase in staff forms. The

TABLE VIII.—NEPHRITIS WITH PYELITIS.

M. G., female, aged four years.

Date.	R. B. C.	Hb.	W.B.C.	B.	E.	M.	Mt.	St.	S.	Ly.	Mo.
June 19	3,750,000	60	25,600	..	..	..	2	13	55	20	10
27	3,300,000	55	25,800	..	..	..	..	12	68	14	6
29	...	..	29,700	..	..	..	..	9	74	13	4
July 1	3,520,000	53	38,200	..	..	..	2	7	61	27	3
2	...	..	23,000	..	..	..	2	7	70	16	5
3	...	..	38,000	..	..	..	..	14	66	20	
6	...	..	...	..	..	..	1	16	48	34	2
7	...	..	23,400	..	..	..	3	5	48	35	9
8	...	..	...	..	1	..	..	9	67	16	7
15	...	..	15,700	..	1	..	1	3	60	35	
18	4,000,000	64	10,500	..	1	..	..	5	50	44	
30	3,760,000	60	15,600	..	..	..	..	1	55	42	2

Table VIII shows rise in the number of immature cells that always preceded and lasted through the period of increased temperature.

TABLE IX.—PERFORATED APPENDIX, PERITONITIS.

R. C., female, aged four years; operated upon, August 24, 1926.

Date.	R. B. C.	Hb.	W.B.C.	B.	E.	M.	Mt.	St.	S.	Ly.	Mo.	
Aug. 25	3,450,000	60	5,800	..	..	1	2	35	40	17	5	Neutrophils degenerated.
26	3,780,000	65	5,900	..	..	..	3	37	45	12	3	
27	3,720,000	65	6,600	..	..	..	3	35	37	23	2	
28	3,450,000	65	7,800	..	..	..	1	37	30	21	3	
30	3,490,000	60	11,100	..	..	..	2	27	40	30	1	
31	...	..	...	..	..	..	2	19	48	40		
Sept. 1	...	..	13,300	..	..	..	4	32	40	34		
2	...	..	18,800	..	..	..	..	23	48	29		
3	...	..	14,000	..	..	..	2	25	50	23		
4	...	..	...	..	..	..	..	20	55	21	4	Drainage of residual abscess.
6	...	..	...	..	..	2	5	33	49	11		
7	...	..	...	..	..	..	1	35	37	23	4	
8	3,050,000	60	8,400	..	..	..	..	20	38	42		
10	...	..	9,000	..	2	..	2	26	34	31	5	
12	...	..	9,200	2	..	..	..	31	30	33	4	
14	...	..	6,200	..	..	..	2	20	42	28	8	
15	...	..	...	..	..	1	..	14	38	45	2	
21	...	..	...	2	..	..	..	7	41	43	7	

Table IX shows stormy course with final recovery.

TABLE X.

Name.	Age, yrs.	Diagnosis.	R. B. C.	Hb.	W.B.C.	B.	E.	M.	Mt.	St.	S.	Ly.	Mo.
E. K.	36	Gall stones	4,800,000	65	7,600	..	5	..	..	2	63	30	
P. R.	32	Kidney stones	4,600,000	70	11,000	..	..	..	..	4	74	22	
R. Mc.	28	Polyarth.	...	..	5,000	..	1	..	..	3	52	44	
I. R.	20	C. C. V. D.	...	..	4,300	..	2	..	..	2	51	44	
S. Z.	5	Mastoid postoper.	4,860,000	70	11,000	..	..	..	2	4	49	46	
M. F.	23	Nephritis	4,080,000	60	7,400	..	..	..	..	1	56	43	1
E. T.	54	Arteriosc.	4,850,000	70	8,700	..	..	..	..	1	62	35	2
M. W.	40	Gastric ob.	4,800,000	75	4,800	..	..	..	..	1	74	24	1
L. A.	39	Card. renal	...	..	9,000	..	..	..	..	1	68	30	1
E. G.	28	Circumcis.	4,560,000	90	5,300	..	..	..	..	..	60	35	5
E. W.	12	Dis. tons.	5,280,000	95	8,000	..	..	..	..	1	61	38	
H. K.	32	Aur. fibr.	5,400,000	90	9,400	1	..	..	..	2	79	17	1
P. K.	38	Hernia	4,480,000	80	11,000	..	..	..	..	3	76	19	2
M. G.	32	Dev. sept.	5,080,000	90	12,000	..	..	..	..	1	72	27	.
J. S.	19	Chr. app.	4,620,000	75	11,900	..	..	..	..	1	70	28	1
J. S.	45	Hypertens.	4,650,000	85	12,400	..	..	..	..	2	71	24	3
W. B.	37	Peptic ulc.	4,200,000	80	10,800	1	..	..	..	3	79	17	
M. W.	44	Ca. colon	3,680,000	70	9,400	..	..	..	..	2	84	14	
M. S.	40	Diabetes	6,350,000	80	7,300	..	..	..	..	5	59	36	
L. S.	38	Fibroids	4,880,000	80	7,600	..	..	..	..	4	63	32	1
M. H.	29	Fr. femur	4,080,000	80	6,200	..	..	..	..	5	61	30	4
C. B.	58	Apoplexy	4,560,000	75	3,200	..	..	..	..	2	58	40	
M. K.	17	Chorea	3,200,000	65	5,600	..	..	..	..	4	53	43	
M. P.	64	Ad. pros.	...	..	7,300	..	..	..	..	3	66	31	

Table X shows a few conditions associated with the normal percentage of immature neutrophils (3 to 5 per cent).

patient then developed a fecal fistula which gradually disappeared. With open-air treatment and forced feeding the resistance of the patient was gradually increased. As the patient was improving clinically, the staff count was gradually dropping (Chart 9).

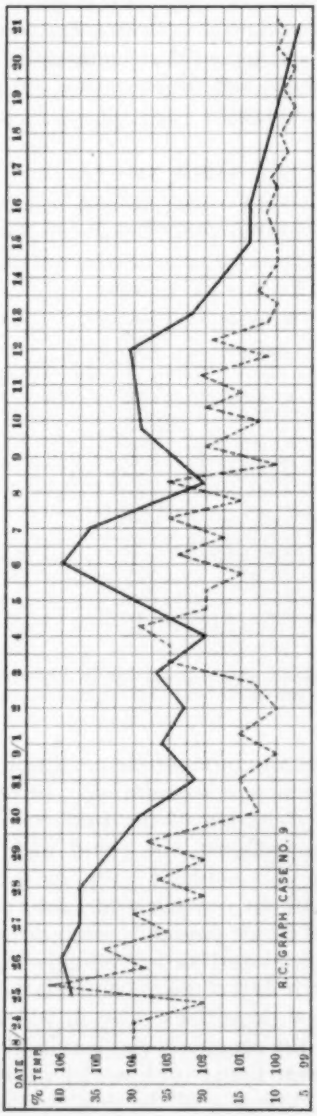

CHART 9

Table X contains a number of conditions in which there is a slight or, in most instances, no stimulation of the bone marrow.

The latter cases can be classified under the noninfectious operative class. Thus new growths, repair of hernias and so forth give the normal number of staff forms, from 2 to 5 per cent, while a catarrhal appendix or a case of cholelithiasis only gives a slight stimulation, such as 7 to 10 per cent. The limited number of acute rheumatic fever or rheumatoid affections have demonstrated very slight immature cell increases. Carcinomas that metastasize to bone, or that start undergoing autolysis and degeneration, do give considerable evidence of marrow stimulation.

TABLE XI.

Name.	Age, yrs.	Diagnosis.	R. B. C.	Hb.	W.B.C.	B.	E.	M.	Mt.	St.	S.	Ly.	Mo.
A. T.	34	Tb kidney	...	..	12,000	..	..	..	..	14	65	21	
R. S.*	3m	Harelip, pn.	...	..	...	..	..	3	10	39	26	20	3
L. B.	28	Tubercul.	4,100,000	75	12,800	..	..	1	3	42	34	17	3
P. F.*	48	Sarcoma, rtp.	...	..	16,000	..	..	..	..	12	76	12	
W. F.*	62	Lung absc.	3,600,000	65	7,300	..	..	..	3	26	45	20	1
M. F.*	34	Malig. end.	...	..	...	..	..	..	..	28	40	19	12
L. D.	8	App. absc.	...	..	8,400	..	..	..	..	22	66	12	
D. E.	9½	Ac. app.	4,720,000	70	24,400	..	..	..	1	13	80	3	4
E. S.*	33	Ly. leukem.	2,720,000	41	42,700	..	..	6	..	5	1	82	
R. L.	30	Lobar pn.	...	..	35,000	..	..	..	2	19	62	15	4
H. K.	27	Sinusitis	4,800,000	80	5,300	..	..	..	..	8	41	40	11
M. E.	29	Ischiorect. abscess	3,850,000	75	13,200	..	..	..	..	11	84	4	1
A. H.	17	Typhoid	3,840,000	72	7,000	..	..	..	..	15	24	58	3
J. F.	22	Influenza	4,480,000	80	9,300	..	..	..	..	11	62	21	6
T. H.*	34	Subac. bact.	...	..	10,400	..	..	..	3	28	48	19	2
J. G.	56	Cellulitis, rt. hand	3,060,000	55	9,900	..	..	..	3	14	75	8	
R. G.*	12	Sepsis	3,480,000	45	16,500	..	..	..	..	18	71	6	5
M. G.	4	Pyelitis	3,360,000	55	15,600	..	..	..	..	10	56	32	2
R. C.	4	Perf. app.	3,720,000	65	6,600	..	..	1	2	35	40	17	5
A. B.	5½	Inf. arthr.	4,720,000	70	23,300	..	..	..	..	24	67	9	
S. A.	13	Sinus thr.	4,800,000	60	14,400	..	..	..	..	26	69	4	1
W. A.*	1½	Mastoid empyema	3,900,000	60	15,000	..	..	..	..	32	35	31	2
H. M.*	24	Lobar pn.	5,500,000	80	5,800	..	..	..	3	38	47	12	

Table XI shows a number of conditions associated with moderate to marked increases in the immature (metamyelocytes and segmented) neutrophilic leukocytes.
* Died.

Table XI has a list of a number of the conditions that are accompanied by moderate or severe stimulation. In none of these conditions was prolonged elevation of the staff count conducive to a good prognosis. In pneumonia one could find the peak of the chart of the immature cells coincide with the period of the crisis. If the patient went without complications into convalescence one could watch the unripe forms gradually drop down to their normal level. When a case developed an exceedingly high staff count in the second to the fourth day of his pneumonia he rarely survived. With comparatively few exceptions cases in which the young cells rose about 50 per cent the prognosis was inevitably fatal. In these cases the neutrophils were found to show definite signs of degeneration, as evidenced by clumping of the granules in the protoplasm, presence of irregular vacuoles in the protoplasm, poor and irregular stainings of the nuclei and occasionally, by complete dissolution of the nucleus. Case E. S. was of marked interest, as it showed

a severe bone marrow reaction and Linksverschiebung in a lymphatic leukemia that had developed a severe pneumonia. Of the 18 neutrophils present, only 1 was a normal segmented form; of the other 17, 6 were myelocytes, 6 were metamyelocytes and 5 were staff forms. Typhoid fever shows the interesting combination of a leukopenia, a high staff and high lymphocyte count. Whereas a catarrhal appendix shows very slight rise, we find that a perforated appendix generally shows an extremely marked rise in the abnormal cells. These cases generally have a stormy and prolonged course, as shown by the chart.[9]

In all of the tables and charts described above I have tried to demonstrate a definite relationship between the course and prognosis of the disease process and the course of the immature neutrophil cell count. Before starting to summarize the value that this classification offers us, I wish to show that this scheme can often also be of value in differential diagnosis.

Case X.—M. B., male, aged ten years, entered the hospital, complaining of abdominal pain, severe headache and temperature. The patient had just returned from some locality outside of the city, where several people had been complaining of abdominal cramps. Two of the patient's sisters apparently also had similar complaints. The child had been sick for almost a week. He had five to six loose, greenish bowel movements daily and temperature up to 104. Physical examination revealed a youth markedly flushed, sensorium tending to be drowsy. The abdomen showed no rigidity; tenderness all over the abdomen and slight rebound tenderness. Differential diagnosis rested between perforated appendix or typhoid. The temperature on admission was 104° F. The blood count taken showed: Leukocytes, 9600; staff, 22 per cent; segmented, 57; lymphocytes, 16; monocytes, 5 per cent. On account of the high staff count and the low lymphocyte count a diagnosis was made of a perforated appendix. Operation revealed a perforated appendix. After operation the staff count gradually returned to normal and patient made an uneventful recovery.

Case XI.—L. B., male, aged five years, entered the hospital with a temperature of 103° F., complaining of severe pain over the lower third of the right leg. The leg was swollen, red and extremely tender to touch. Was it an osteomyelitis or a soft tissue abscess? The blood count was: Red blood cells, 4,160,000; hemoglobin, 70 per cent; leukocytes, 22,700; metamyelocytes, 2 per cent; staff, 3 per cent; segmented forms, 67 per cent; basophils, 2 per cent; lymphocytes, 26 per cent. A count not in favor of an osteomyelitis would more likely go with an abscess not involving the bone marrow. Operation revealed a deep soft tissue abscess. Temperature dropped after incision and drainage, and child recovered.

Case XII.—S. B., male, aged seventy-three years, entered the hospital with a history of three days of abdominal cramps; no vomiting. The temperature was 103° F.; pulse, 98; no hypertension. Physical examination revealed a markedly rigid abdomen; pain and tenderness not marked. The blood count showed: Leukocytes, 14,000; staff, 28 per cent; segmented forms, 69 per cent; lymphocytes, 3 per cent. The diagnosis was perforated appendix. The operation showed perforated appendix with peritonitis. With subsequent counts the staff forms gradually returned to normal.

CASE XIII.—R. G., female, aged thirty-six years, entered the hospital, complaining of severe headache, fever and constipation. This had lasted for about a week. The headache would occasionally subside for a short while, but would reappear. The temperature on admission was 103.8° F.; pulse, 80; respirations, 28. Was the case typhoid or not? The blood count revealed the following findings: Red blood cells, 5,120,000; hemoglobin, 75 per cent; leukocytes, 8100; staff, 4 per cent; segmented forms, 57 per cent; lymphocytes, 39 per cent. The count is not that of typhoid. The patient left the hospital in one week completely recovered.

Comment. Up to the present time the interest in a blood count generally centered itself in the total leukocyte count and the percentage of neutrophils. It is therefore very easy to understand the reason for the lack of interest in the leukocyte picture that has been gradually developing in the profession at large. The total count and the percentage of neutrophils in themselves are not the main points of information, and thus men only interested in these two points find themselves very often disappointed. Using the total white count as an index of good resistance and the other as an index of infection, surgeons and physicians could not understand why the blood count did not coincide with the clinical picture. In a ruptured appendix, where they expected to get a count of at least 20,000, they would get 6000, and the medical man expecting a pneumonia to have 25,000 would get 9000. The medical man, trying to get around this sore point, finally decided that the invading organism was the cause of the high or low count, and to a certain extent he was right.

I have found that the exact number of leukocytes was of relatively small importance. It makes very little difference whether the total count is 20,000 or 15,000. As far as the leukocyte count is concerned, we are interested in one of three points. Is it a leukocytosis, normocytosis or leukopenia? The old view that a hyperleukocytosis means good resistance and a leukopenia poor resistance is no longer tenable. The number of leukocytes that the bone marrow sends into the blood stream is mainly dependent on the type of bacterial toxin and the reaction of the bone marrow to it. If the toxin stimulates it we have a hyperleukocytosis of the regenerative variety. It is in this type that Schilling claims the Jungkern or metamyelocyte and the myelocyte are to be found. In the other type of toxin, as exemplified by the toxins of typhoid, influenza and certain streptococci there is an inhibition of the bone marrow with a resultant leukopenia. This type Schilling terms as degenerative. There is also a mixed type, a regenerative-degenerative. While in the purely degenerative type there are no metamyelocytes, the mixed type may have them. After knowing whether one is dealing with hyperleukocytosis, normoleukocytosis or hypoleukocytosis, the next and most important item is: What is the character of the individual cells? By a careful study of their character we will find that the significance of the blood counts will rise and that when

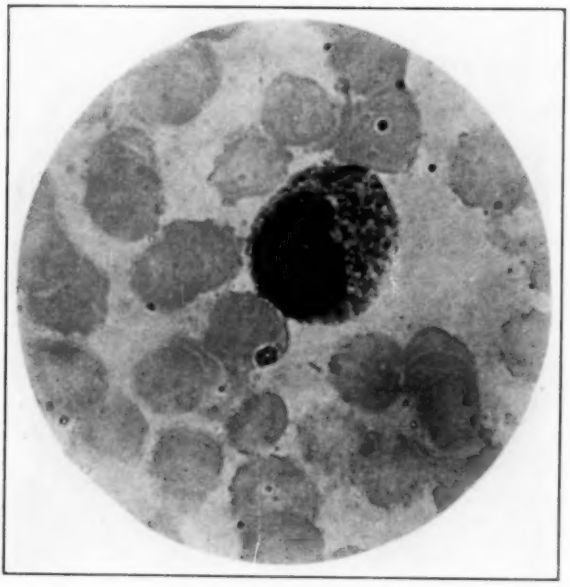

FIG. 1.—Metamyelocyte.

FIG. 2.—Staff or rod form. (Stabkernige.)

FIG. 3.—Staff or rod form with double twist.

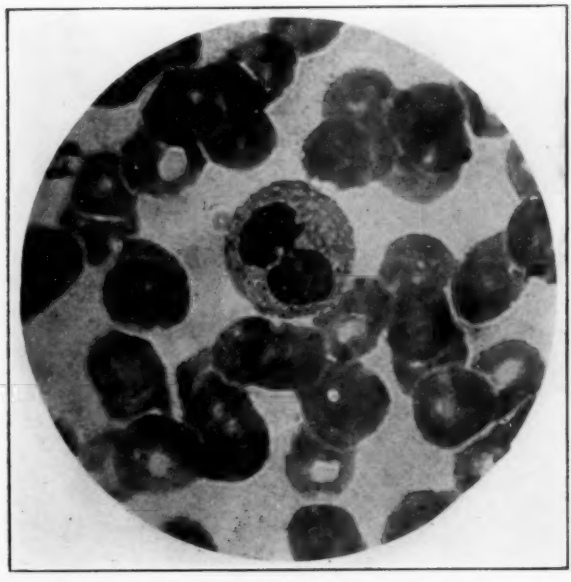

FIG. 4—Segmented form—note tail of lower segment definitely to right of upper segment.

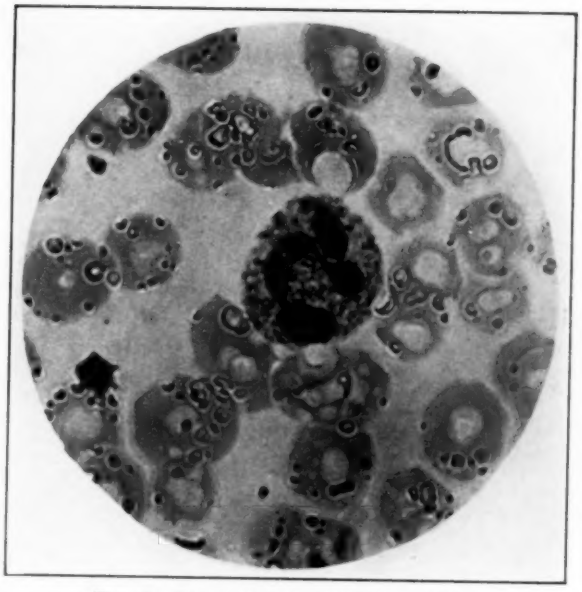

FIG. 5.—Segmented form (four segments).

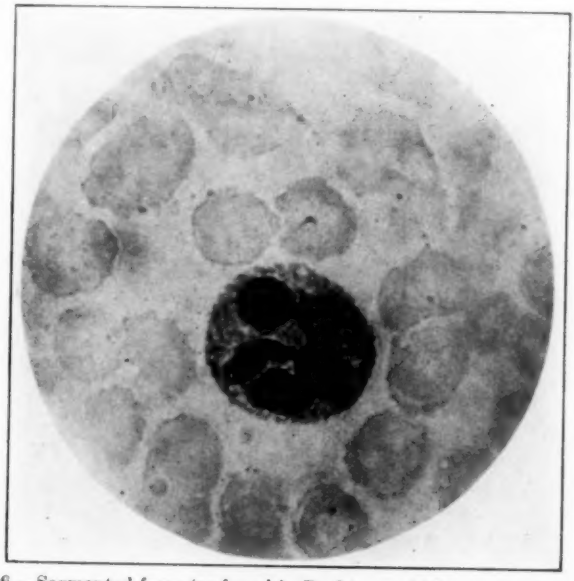

FIG. 6.—Segmented form (as found in Rechtsverschiebung—in P. P. A.).

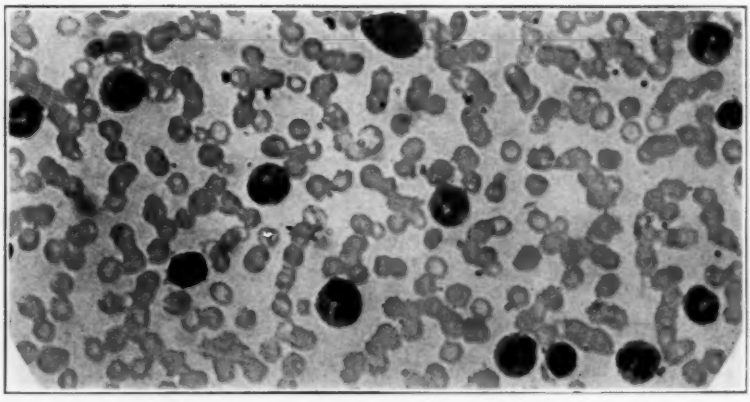

FIG. 7.—Extremely high percentage of young neutrophils (39 per cent) in a case of empyema. Died on same day that smear was taken.

interpreted in conjunction with the clinical picture much information of value will be gleaned therefrom. By daily study of the immature cells the course of the disease can be mapped out more easily and the prognosis discerned. In surgical cases a high staff count acts more or less like a pus indicator. During postoperative care a high count means that all is not well, and that some complication or residual abscess is to be dealt with. In medical cases a rise in the staff count after it has begun to drop or a steady high level means a complication. An apparently ordinary bronchitis, with a high staff count, is most often tuberculous.

Conclusions. With a limited amount of material (1000 blood examinations), I have been able to draw the following conclusions.

1. With the height of infection there is a concomitant peak to be observed in the number of immature leukocytes.

2. As the disease process tends to lessen and convalescence sets in there is a drop of the "staff" forms to the normal quota (3 to 5 per cent).

3. Persistence of the high level of "staff" forms means some complication.

4. Crisis in pneumonia is very often accompanied by a "staff" count approaching 50 per cent of the total leukocyte count.

5. Presence of a count nearing 50 per cent of immature forms during the early days of a pneumonia means generally a fatal prognosis.

6. The chart of the immature cells coincides often more accurately with the course of the illness than the temperature.

7. The percentage of immature cells is by far more valuable than the total leukocyte count or the percentage of neutrophils.

8. The method employed is simple and does not take more time than universal methods do. In those cases where two or three counts a day are required so as to follow the case throughout its course it is not necessary to do a complete count each time. A complete count is done in the morning and thereafter smears can be taken every two or three hours if necessary and the differentials done at one's leisure. It is often not necessary to do a leukocyte count more than once a week. Due to the large percentage of error that one encounters in consecutive leukocyte counts, and because I have found it to be of less value than the percentage of staff forms, I very often make one total count and then follow the case by its differentials.

I do not wish to leave the impression that I believe this method to be 100 per cent perfect. Of course it is not. Up to the present I have not been able to account for low staff counts in some appendix and gall bladder cases and so forth. If we reason that it is due to the fact that the bone marrow is not stimulated by those toxins, we cannot explain why one toxin does and the other toxin does not.

I believe that this classification is of definite value, but it is only

by its extensive application that it shall be determined whether this procedure is with us to stay. It was with the hope that this paper would serve as a stimulant to others, that I publish this preliminary report.

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ROSACEA.

With a Study of Accompanying Conditions.

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Reference to textbooks on dermatology discloses a consensus of opinion that rosacea is commonly associated with derangement of the gastrointestinal tract. A few authors even venture the statement that it is secondary to this digestive fault. All, however, are content to advise a search for abdominal trouble and give no hint as to what will be found.

Since the old term "acne rosacea" persists, it becomes necessary to differentiate acne from rosacea before proceeding. Clinically, acne is recognized by the presence of seborrhea, comedones and pustules; rosacea by erythema, telangiectasia and papules, sometimes becoming pustular. Acne begins with an overactivity of the sebaceous glands, rosacea as a transient dilatation of the cutaneous bloodvessels. The sequence of events is exactly the reverse of that in acne vulgaris since the hypertrophy of the sebaceous glands in rosacea develops only after the congestion has become marked and permanent. Acne is a disease of the second and third decades of

life; rosacea does not begin until the fourth. Acne is distributed over the face, neck, shoulders, back and chest; rosacea is limited to the flush area of the face. The "primitive lesion" of acne is the comedo, that of rosacea is capillary dilatation. Acne usually dies out, even without treatment, by the time the patient reaches the age of thirty-five years, while rosacea, at that age, is just becoming sufficiently pronounced to annoy the patient, is permanent and is slowly progressive unless adequately treated.

The two diseases, then, have only the most superficial resemblance and the designation "acne rosacea" is inept. It is preferable to speak of acne vulgaris and rosacea as two distinct diseases having no etiologic kinship. In the occasional instances in which persistent acne is complicated by the development of rosacea, the diagnosis should be acne and rosacea, not acne rosacea.

The work here reported was undertaken at the Cornell Clinic in the hope that more or less constant findings might be made a basis for improvement upon the empiric internal treatment of rosacea now commonly used.

Rosacea constitutes 3 per cent of all skin diseases (Stelwagon). It is more common in females than in males, the proportion usually mentioned being 5 to 1 or 6 to 1. Of 135 cases analyzed for this paper, 90 occurred in females and 45 in males—a ratio of 2 to 1. In this series, the average age at which the disease was first noticed was 31.3 years in females and 33.7 years in males. Females do not apply for treatment until the disease has been present 4.7 years and males delay even longer. This observation is interesting in that it shows how gradually rosacea develops and because this delay in seeking treatment renders almost impossible efforts to determine the sequence of appearance of associated conditions.

Of the women 37 per cent were unmarried; of the married women 58 per cent had borne children. Two-thirds of the 90 females in this series were childless at the average age of thirty-six years. Two-thirds of these patients were of north-European ancestry. No adequate notes of complexion are available. A number of cases were observed in very dark individuals and one patient was a negro.

In addition to gastrointestinal defects, a number of other factors have been mentioned as commonly present in cases of rosacea. Exposure to sunlight, wind and to extremes of heat and cold, the presence of nasal polypi, chronic rhinitis and pharyngitis, pyorrhea, root abscesses, chronic tonsillitis, pelvic congestion and functional or organic ovarian disease have been frequently suggested.

Although a number of the cases analyzed occurred in males leading an outdoor life, the percentage of cases in which this factor must be considered was very small: the preponderance of cases in females tends to show that, while exposure to the elements may aggravate the condition, it is not basic. Many of these cases were referred to nose and throat and to dental specialists for examination. The

findings are not important considering their total number. Gynecological examination of all cases complaining of pelvic disturbances were undertaken. In this department, again, there was no uniformity of findings, only a moderate number of instances of salpingitis, cervicitis and ovarian dysfunction being noted. In the few patients operated upon for repair of lacerations, the gynecologist usually stated that the benefit expected was largely local and not likely to influence the rosacea.

A less stable nervous balance, a weak peripheral circulation (MacLeod) and a greater liability to indigestion and constipation in females have been suggested as reasons for the higher incidence of rosacea in women. These factors may have some weight, but the findings relative to the generative organs of women in this series gives little support to the theory that women with rosacea are frequently sufferers from pelvic disease.

Thirty-five cases were subjected to a general medical examination and here the results showed a certain uniformity. Two-thirds of these patients were found to be underweight. Low blood pressure was noted in about the same proportion. The next most common finding was poor muscular tone, especially of the abdominal muscles. The presence of neurasthenia, nervousness and hysteria was commonly noted. Five of these cases were found to have arthritis or rheumatism, 1 had a chronic prostatitis, 1 patient was an old syphilitic and 2 were old alcoholics.

One case was diagnosed hyperthyroidism and 2 hypothyroidism. Basal metabolism tests on these patients showed no marked deviation from the normal.

Fifty cases were subjected to a complete gastrointestinal examination. Fluoroscopy disclosed surprisingly few organic abnormalities; a case of inoperable cancer of the stomach, an old, healed, postpyloric ulcer, and one of duodenal adhesions. However, 17 of the 50 patients had visceroptosis, and 22 chronic constipation. Most of the functional disturbances were of the large intestine, spastic conditions being commonest.

Test meals in these 50 consisted of a shredded wheat biscuit and 2 glasses of water. The stomach contents were removed after an hour and a gastric analysis was made. A tabulation of the acid findings follows. Only once was the presence of excessive mucus observed, so that gastric catarrh should not be considered a factor in the interpretation of the findings.

These 50 cases may be divided into the following groups:

Complete achlorhydria 7 cases, 14 per cent (no free HCl).
Marked hypochlorhydria 17 cases, 34 per cent (free HCl below 20).
Slight hypochlorhydria 11 cases, 22 per cent (free HCl 20 to 30).
Normal acidity 10 cases, 20 per cent (free HCl 30 to 45).
Hyperchlorhydria 5 cases, 10 per cent (free HCl 45 and upward).

TABLE I.—GASTRIC HYDROCHLORIC ACID IN ROSACEA. (50 CASES.)

Number.	Total acidity.	Free HCL.
1	37	28
2	26	15
3	30	20
4	12	8
5	..	0
6	10	0
7	6	0
8	38	26
9	38	27
10	18	12
11	57	45
12	26	20
13	38	26
14	16	6
15	16	10
16	36	28
17	60	50
18	16	10
19	6	0
20	74	60
21	46	33
22	50	38
23	45	30
24	6	0
25	30	19
26	26	18
27	22	10
28	49	40
29	23	17
30	50	43
31	35	24
32	20	11
33	10	0
34	53	43
35	18	9
36	26	15
37	40	30
38	11	5
39	46	33
40	32	14
41	41	29
42	40	28
43	30	22
44	8	0
45	63	49
46	43	31
47	60	38
48	69	56
49	19	8
50	20	8
Average	31.8	21.8

Late in 1920, Ryle and Barber published a paper on "Gastric Analysis in Acne Rosacea"[1] in the *Lancet*. Having noticed that the tongues of rosacea patients were usually broad, flabby, pale and markedly indented at the edge, and having associated this appearance with hypochlorhydria, they gave their patients dilute hydrochloric acid and noticed rapid improvement. They then

subjected 12 patients, all females, to fractional gastric analysis. Five were found to have complete achlorhydria and 2 others an extreme degree of hypochlorhydria; of the remaining 5, 1 showed no free hydrochloric acid until after one hour and 2 showed a temporary high peak in the curve of acidity with an abrupt fall to the base line. Thus 10 of their 12 cases presented abnormal types of acid curve, and, of these, 7 (58.3 per cent) showed extreme hypochlorhydria. Using the same technique they found hypochlorhydria present in 20 per cent of other dyspepsias and in 10 to 12 per cent of apparently healthy male subjects.

Bell,[2] in a large series of fractional gastric analyses, including other than dyspeptic diseases, found normal acid curves in 61 per per cent while hyperchlorhydria was noted in 24 per cent and hypochlorhydria in 15 per cent.

Brown,[3] also using the fractional method of gastric analysis, examined 50 cases of rosacea and 50 cases of other dermatoses. His analysis of these cases is as follows:

TABLE II.—BROWN'S GASTRIC ANALYSES IN DERMATOSES.

	Rosacea (50 cases).		Other dermatoses (50 cases).	
Gastric juice.	No. cases.	Per cent.	No. cases.	Per cent.
Complete achlorhydria (no free HCl)	7	14	6	12
Marked hypochlorhydria (free HCl below 20)	8	16	5	10
Slight hypochlorhydria (free HCl 20 to 30)	13	26	9	18
Normal acidity (free HCl 30 to 45)	18	36	17	34
Hyperchlorhydria	4	8	13	26

Combining Brown's 50 rosacea cases with the 50 examined for this paper, and disregarding the difference in the technique employed, it appears that of 100 cases of rosacea subjected to gastric analysis 14 had complete achlorhydria, 25 marked hypochlorhydria, 24 slight hypochlorhydria, 28 were within normal limits and only 9 had hyperchlorhydria.

Seventy per cent of the cases here reported had subacidity: 56 per cent of Brown's cases were subacid, and 58 per cent of Ryle and Barber's cases. Combining all the cases (112), 19, or 17 per cent, failed to show a trace of free hydrochloric acid. From these figures, it appears that about two-thirds of patients with rosacea also have subacidity and that in one-third of these the defect has reached the stage of achlorhydria.

The significance of markedly diminished or absent hydrochloric acid seems to be in dispute. Some authorities point out that achlorhydria is present in 5 per cent of apparently healthy individuals. Ryle[4] thinks that "neither hypochlorhydria nor achlorhydria can in themselves be regarded as pathological findings."

Bennett[5] says, "A person without hydrochloric acid is deprived of: (1) A useful but accessory agent for protein digestion; (2) a useful

but accessory agent for controlling the gastric sphincters, and (3) an important but not essential means of diminishing bacterial growth in the intestines."

On the other hand, Faber,[6] in his recent lecture on the etiology and pathogenesis of achylia gastrica, maintains that symptomless achlorhydria is not a valid argument against its abnormality since many severe conditions are often symptomless and because he believes that sooner or later symptoms do develop in cases of achylia gastrica. He points out that Chiewitz and Anderson failed to find anything that could be regarded as congenital achylia in the examinations of 127 children. He believes that achylia gastrica in children usually is preceded by some parenteral febrile disturbance or by affections of the gastrointestinal canal, particularly the varieties of infectious enteritis.

Faber does not believe it has been demonstrated that patients with achylia gastrica belong to a group characterized by congenital weakness and maintains that while "we may sometimes see a passing achylia of nervous origin, a chronic achylia arises either by direct injury to the stomach or by hematogenic intoxication." One point strongly emphasized by this author is that achylia, once established, tends to persist and is, therefore, more likely to be present with increasing years. Seidelin, he points out, found secretion absent or greatly diminished in 40 per cent of the working class above the age of fifty years; in old persons of sixty-seven to ninety-two years there was anacidity in 67 per cent.

He concludes that the natural term for the disease is gastritis, by which is to be understood, not the old conception gastric catarrh, but a disease of the glandular parenchyma of an inflammatory nature analogous to nephritis or hepatitis.

The list of diseases in which gastric hydrochloric acid is absent or greatly diminished is impressive and should be considered in assaying the importance of this symptom. It is headed by pernicious anemia and subacute combined degeneration of the spinal cord (where achlorhydria is always present) and includes cancer of many different organs, chronic gastric catarrh, cholecystitis, typhoid infections, dysenteries, intestinal parasitic infections, sprue, pellagra, tuberculosis, chronic nephritis, gout, multiple infectious arthritis, myocarditis, syphilis, Graves' disease, diabetes mellitus, malaria and Glénard's disease.

In pregnancy, diminished gastric secretion is found in 86 per cent of cases during the last few months before labor. During menstruation, the secretion is subnormal. This last observation, perhaps, should be borne in mind when trying to account for the exacerbations of rosacea commonly noted during the menses.

When gastric hydrochloric acid is absent or greatly diminished, defective control of the gastric sphincters becomes common and there is a tendency to rapid emptying. The antiseptic action of the

gastric juice is decreased and germs ordinarily destroyed in the stomach pass to the intestine in a viable state. Stimulation of the duodenal mucosa by the normal acid gastric contents is lost, and the proteins in the meal pass into the intestine without having been adequately altered by gastric digestion.

The sum of these factors tends toward intestinal indigestion and it is not surprising to note that Schwartz[7] found, in examination of the stools of 101 cases of rosacea, only 36 within normal limits. Protein putrefaction was marked in 31 cases, and carbohydrate fermentation in 34. The percentage of abnormal findings in rosacea was higher than in any other of the large number of skin conditions in which Schwartz tabulated stool examinations. Such evidence of intestinal indigestion would logically be expected in the light of the frequent finding of constipation, visceroptosis and dysfunction of the large bowel noted in the fluoroscopic examinations already mentioned.

An evaluation of the significance of the internal abnormalities disclosed by this investigation cannot be offered with any degree of assurance. No convincing evidence indicates what deviation from the normal first occurred. The duration of none is known, with the exception of the rosacea. Furthermore, as was pointed out above, rosacea patients delay seeking advice for four or five years so that it is conceivable that some of the internal troubles may not have been present when the disease was first noticed. The observation has been frequently made that rosacea patients display a fondness for gastric stimulants in their choice of food, and this has been suggested as one of the causes of the condition. It may well be that the craving for irritants is a compensatory habit resulting from the lack of adequate hydrochloric acid production and that if correction of the deficiency were possible by such means the chosen diet would prevent rather than produce rosacea.

In the same way, the conclusion that those afflicted with rosacea belong to a highly neurotic type of humanity characterized by a hair-trigger vegetative nervous system, while probably true, cannot be unhesitatingly accepted as an explanation of the condition found. This nervous element may be a result rather than a cause of the other abnormal conditions.

The prompt flushing of the face following the ingestion of tea, coffee, alcohol, condiments, meat extractives or food taken at too high a temperature, often noted by patients with rosacea is good evidence that stimulation of the gastric mucosa has a reflex dilator effect on the bloodvessels of this area. As a matter of fact, a reflex path through the vegetative nervous system can be readily mapped out on an anatomical basis (though it is not easy to determine that the route selected is the one actually followed). If, however, rosacea occurs only in patients with a poorly balanced vegetative nervous system, it is difficult to explain the defect on this basis, for

flushing of the face is a vagotonic symptom, and vagotonics usually have pronounced hyperacidity. These cases can be classified as vagotonic only on the assumption that initial hyperacidity has been succeeded by subacidity or achlorhydria following an exhaustion of the gastric secretory cells. Although subdivision of the cases reported here leaves totals too small for statistical weight, it is suggestive to find that the average age and average duration of the rosacea increase as the gastric hydrochloric acid content diminishes, thus:

TABLE III.—RELATION OF GASTRIC ACIDITY TO AGE AND DURATION OF DISEASE.

	Age.	Duration.
Hyperchlorhydria	35	1 yr. 5 mo.
Marked subacidity	37	3 yrs. 3 mo.
Achlorhydria	48	5 yrs.

It may be that cases of rosacea fall into a group that might be described as "visceral defectives," prone to visceroptosis (Hunter[8] found achlorhydria in 70 per cent of cases of visceroptosis), chronic constipation, stasis, and a resultant indigestion with absorption of poisonous products from an abnormally permeable intestinal mucosa. The theory supposes that members of the group, in spite of their handicaps do fairly well during their first twenty or twenty-five years but that soon afterward life becomes too great a strain and they begin to break down.

This theory may have merit, but before accepting it one would look for stronger evidence of the appearance of rosacea in families and of its being more distinctly limited to a certain type of individual. Also one would expect such patients to become incapacitated within a few years after developing rosacea.

It is apparent that the data available is insufficient to warrant a statement as to the etiology of rosacea. Two things, however, seem permissible, first the construction of a hypothetical case giving a composite picture of the most common associated signs and symptoms of the condition, and second some suggestions as to treatment.

A worried woman, aged thirty-six years, somewhat under weight, and with a faulty posture, will be the typical patient. She has noticed an increasing redness of her nose and cheeks for a period of four or five years, with an occasional papule, and dilated vessels at the angles of the alæ nasi and possibly on the cheeks. Occasionally a few of the papules have become pustular, but not many comedones are present. The orifices of the sebaceous glands of the nose and adjacent cheeks are patulous, and the skin is oily. These changes are confined to the hyperemic areas.

The progress of the trouble has been so gradual that she has not previously sought advice. She volunteers no statement as to her general health, but on questioning her it will be found that she is

not muscularly strong, that she is extremely nervous, that she is constipated and that she occasionally has vague abdominal discomfort. She says that she has a poor appetite but admits that she takes tea and coffee frequently and that she likes highly seasoned foods. She states that although her work burdens her and she tires easily she does not think of herself as being sick.

Her family history contains nothing pertinent except possibly a statement that her parents were "high strung." None of her brothers or sisters are suffering from rosacea. The patient has had the usual diseases of childhood but does not remember any severe illness since that period.

Examination reveals, aside from the skin condition, a large, pale, flabby tongue, indented at the edges, a slightly enlarged thyroid gland, normal heart and lungs but a lowered blood-pressure. The abdomen shows evidence of visceroptosis but there are no masses or tender areas. The abdominal muscles are markedly relaxed and atonic. The lower extremities are likely to present telangiectasia but varicose veins are not observed.

The patient, when subjected to a gastrointestinal examination, will be found to have a total acidity of about 30 and a free hydrochloric acid content of about 21. She will have visceroptosis, spasticity of the colon and chronic constipation. No organic diseases of the abdomen or pelvis will be found. The rectal examination will probably show congestion or possibly hemorrhoids.

The outstanding features of the case are, first, the skin lesion and then the presence of poor muscle tone, low blood pressure, subacidity, visceroptosis, constipation and nervousness.

Locally the treatment of rosacea does not present great difficulties. After freeing the face from grease, the daily use of an astringent lotion such as lotio alba compound or a weak resorcin or salicylic acid lotion is usually adequate. As the skin toughens, the application must be strengthened until the dilated capillaries have sufficient support to render them invisible. Any remaining larger vessels can be destroyed by electrocoagulation.

Local treatment alone produces considerable improvement. It is probably because of this that so many different forms of internal medication are enthusiastically advocated. Certainly on the facts here presented, a scientific defense of the internal administration of alkalies becomes somewhat difficult and much of the dietetic advice given becomes absurd. In order to obtain permanent or long-continued relief from rosacea, the internal derangements must be corrected, and when this is accomplished lasting results become possible.

It is evident that patients with rosacea should be first subjected to a complete gastrointestinal examination. If subacidity should be found, as will happen in a majority of cases, the patient is likely to make surprisingly rapid progress when this condition is improved

by the administration of large doses of hydrochloric acid. A dram of dilute hydrochloric acid in a glassful of water, possibly with the juice and pulp of an orange added, should be taken gradually during each meal, and this should be the only liquid allowed with food. An adequate fluid intake should be assured by two or three glasses of water a half hour before meals.

Patients with subacidity usually indulge excessively in coffee, tea, alcohol and condiments, and all of these gastric stimulants must be permanently eliminated from the diet. Sauces, gravies, meat extracts and hot meat soups are forbidden. Meats are not contraindicated but should be simply prepared and taken in small amounts only. Vegetables rich in essential oils should be eaten only sparingly while bulky green vegetables should be consumed in abundance. There is no objection to any of the fruits and, since the quantity of meat is limited, a moderate amount of carbohydrates must be allowed. Graded exercise is required to improve the poor muscular condition, and with special attention to the abdominal muscles. Patients with ptosis should wear an abdominal binder until exercise has improved their muscular tone enough to warrant discarding it. Mineral oil is given to relieve the constipation. If the stool volume is small agar flakes in teaspoonful doses are given once daily. Small doses of tincture of nux vomica may be added to the hydrochloric acid to improve nerve tone. This treatment persisted in for several months gives lasting results in most cases.

Summary.—Complete gastrointestinal examinations were made on 50 patients suffering from rosacea. Two-thirds of them were found to have a group of functional abnormalities occurring with sufficient uniformity to suggest that they form an essential part of the disease.

These abnormalities may be grouped as follows: A neurotic tendency, subnormal weight, low blood pressure, poor muscle tone, faulty posture, visceroptosis, chronic constipation, spasticity of the large bowel, and gastric subacidity.

Correction of these conditions together with local treatment results in rapid and lasting improvement in most cases.

NOTE: The gastrointestinal examinations of these patients were done under the direction of Dr. H. H. Fellows, Chief of the Department of Gastrointestinal Diseases, Cornell Clinic.

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MAINTENANCE OF LEUKOCYTE LEVEL AND CHANGES DURING IRRADIATION.

A Study of the White Blood Corpuscles Appearing in the Saliva and Their Relation to Those in the Blood.

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Numerous problems in medicine, both physiologic and clinical, involve some phase of blood production and destruction. Little is known of the actual mechanism by which the formed elements of the blood are removed from the circulation in health. The increase in the products of nuclear metabolism and destruction in leukemia, especially after Roentgen ray therapy (Buckman, Daland and Weld[1]) suggests that many leukocytes undergo their destruction in the body itself. There are, however, many places where white blood corpuscles are lost from the circulation and find their way into different secretions and excretions. Numerous leukocytes* appear in the saliva, the mucous membrane of the mouth being one of the points of exit of the white blood cells. Histologic studies of the mucous membranes of various parts of the gastrointestinal tract have shown the presence of leukocytes, apparently migrating to the surface. Lymphocytes have been noted in gum tissue (Beckwith, Simonton and Williams[2]), in the tonsillar epithelium (Stöhr[3]) and in the gastrointestinal mucosa (Bunting and Huston;[4] Dukes and Bussey[5]). "Endogastric leukopedesis" has been described (Mauro[6]) and the passage of lymphocytes into the mammary alveoli and of neutrophils into the ducts, in correlation with a local circulatory leukopenia, during lactation, has been noted (Emmel, Weatherford and Streicher[7]). An appreciable number of leukocytes pass into the urine of normal individuals during the course of the day (Addis[8]) and considerable numbers find their way through the membranes of the respiratory tract. The white blood corpuscles may be removed from the peripheral circulation fairly rapidly, as shown by the disappearance, within thirty-five minutes, of lymphocytes which had been transfused from a patient with chronic lymphatic leukemia into one with lymphoblastoma in a lymphopenic phase (Minot and Isaacs[9]).

* The term "leukocytes" in this paper is used to include all the types of white blood corpuscles.

The necessity for studying the fate of leukocytes has been emphasized because of the relationship between blood destruction, with occasional leukopenia and Roentgen ray or radium irradiation in cancer, lymphoblastoma, leukemia and other malignant conditions. Therapeutic irradiation is usually followed by a primary increase in the number of white blood cells in the peripheral circulation, lasting one or two days, followed by a decrease of varying duration. The question of the contraindication of Roentgen ray irradiation is sometimes considered when the patient presents a marked initial leukopenia. In these cases it is necessary to know whether cells are being produced, but are rapidly lost, or whether the marrow is aplastic, or hypoplastic, or incapable of delivering cells into the blood stream.

Of the places where white blood corpuscles may be destroyed or lost, those in which visible leukocytes appear in the excretions are the simplest to study quantitatively. The saliva, as it accumulates in the mouth, presents an excellent medium for the study of extruded leukocytes.

Although much attention has been directed to the bacteriology and morphology of the sputum in the routine analysis, comparatively little appears in the literature about the leukocytes of the saliva. In a general way, while it has of course been felt that the numbers of leukocytes increase in purulent infections of the mouth, nose and respiratory tract, no exact quantitative studies of the cells of the normal saliva have been published. A description of the increase in the sputum of the polymorphonuclear neutrophil leukocytes in bronchitis, pneumonia and similar purulent infections appears in textbooks. Reference is also made of the predominance of lymphocytes in certain stages of pulmonary tuberculosis, and the increase of polymorphonuclear eosinophil leukocytes in bronchial asthma and related conditions. No concise description of saliva in these diseases has been recorded.

The present study deals with the white blood corpuscles of the saliva, their number, type, degree of vitality and variations in health and disease, and their behavior after Roentgen ray irradiation therapy. A correlation is made between the number and kind of leukocytes in the saliva and those in the blood. Too many factors enter into the composition of the sputum, in contrast to the saliva, to make valuable quantitative cell studies of the former.

The use of the term "leukocytes of the saliva" probably needs some qualification because the saliva as it appears at the opening of the ducts of the salivary glands is practically free from leukocytes. The leukocytes which appear in the saliva that accumulates in the mouth are gathered from the mucous membrane of the buccal cavity as described below.

Material and Methods. Cells in the saliva are easily crushed, so that fixed films, such as are prepared to observe cells from the blood,

were not found serviceable. Studies of the fresh cells were made by inverting a cover glass, with and without dried stain on its surface, over a small drop of the material to be examined, and sursurrounding the edges with a seal of petrolatum. As stains, brilliant cresyl blue alone, or in combination with eosin, neutral red and Janus green and other dyes were used. Only very small amounts of stain were dried on the cover glasses in order to reduce the toxic action as much as possible. This method permits the study of the intact cells, and the making of differential counts of the various types of leukocytes as well as the relative number of those living and dead (Sabin, Cunningham, Doan and Kindwall[10]).

Counts of the cells per cubic millimeter of the saliva were made by the following method: The individual was asked to gather up all the saliva in his mouth and swallow it. He was then instructed to open his mouth, lift up his tongue and tilt his head slightly forward. The saliva was drawn up from the "pool" which collected in front, at the sides and at the base of the tongue, with a glass pipette. Several drops may be obtained in the pipette, such as is used for counting the white corpuscles of the blood. The material was then blown gently under the cover of a hemocytometer slide and the cells were counted directly under high power of the microscope. The saliva will run under the cover glass with remarkable ease and uniformity, and is usually free from bubbles. Occasionally a more uniform distribution may be obtained by raising and lowering the cover glass. Saliva taken directly from the ducts of the salivary glands usually shows few or no cells, but the fluid which has washed over the mucous membranes of the cheeks or tongue contains numerous leukocytes. It is thought that this method eliminated the errors in counting which would naturally follow when the saliva was profuse or when it was scanty. It was found that fairly comparable results were obtained when the same amount of saliva, washing over a given area of mucous membrane, was allowed to accumulate. The cells, then, which were washed together by about 1 or 2 c.mm. of saliva, were considered in each determination.

The method, at its best, is of course cruder than that used in enumerating the cells in the blood, but the results obtained from the study of several drops from the "pool" were surprisingly uniform, as were the maximum and minimum for normal individuals from day to day. Furthermore, the differences between the cell counts of the saliva of the normal subjects and the patients were so great as to be beyond the range of the technical errors in gathering the saliva and counting its cells.

As the saliva is sometimes quite viscid, and at other times more fluid, care must be taken to include all the cells by using a wide range in focussing the microscope, as the cells may not sink as well as when a diluting solution is used as in enumerating blood cells.

In the individuals studied saliva and blood were taken for examination at the same time, and the time of the day, relation to meals, exercise and other data noted. When multiple counts were made at short intervals the blood was taken from different fingers; otherwise, the lobe of the ear was used.

Saliva of 10 normal individuals was studied repeatedly and under varying conditions and from 68 patients with the following conditions: Chronic myelogenous leukemia, 13; chronic lymphatic leukemia, 9; lymphoblastoma (other types), 24; cancer of the breast, 7; cancer of the uterine cervix, 3; other types of cancer, 6; infections (respiratory, genitourinary), 3; pernicious anemia, 2; aplastic anemia, 1. Repeated examinations of the saliva of these individuals were made, during the course of the day and on many different days before and after treatment and other procedures.

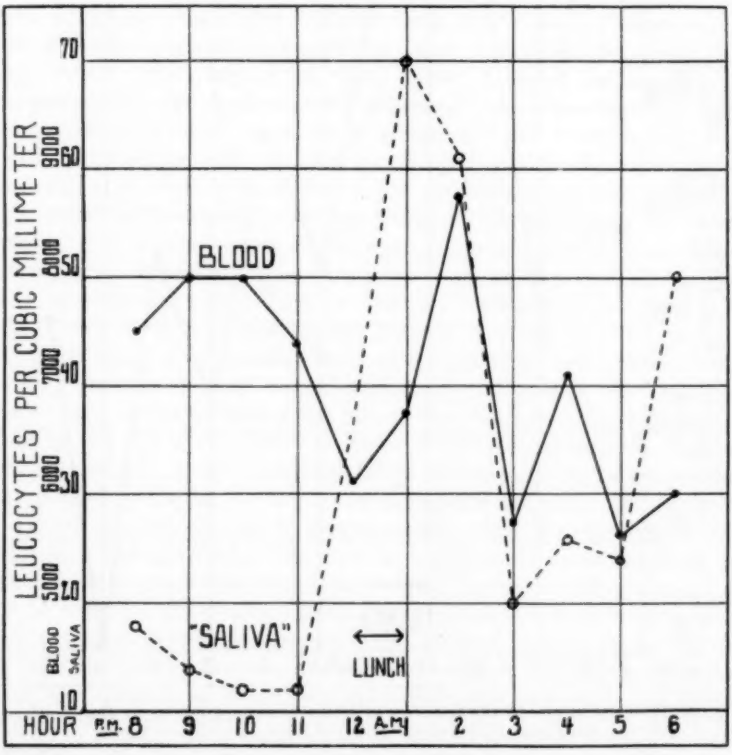

CHART I.—Variations in the number of white blood corpuscles in the blood and saliva of a normal man, working at night, during the course of eleven hours.

Data: Leukocytes in Saliva in Health. The saliva of the normal individuals showed varying numbers of leukocytes at different times of the day. Charts I and II illustrate the variation from hour to

hour in 2 healthy persons with the corresponding counts of the white corpuscles in blood. Very similar data were obtained from numerous other individuals. The striking variation in the number of leukocytes per cubic millimeter of blood from hour to hour, as

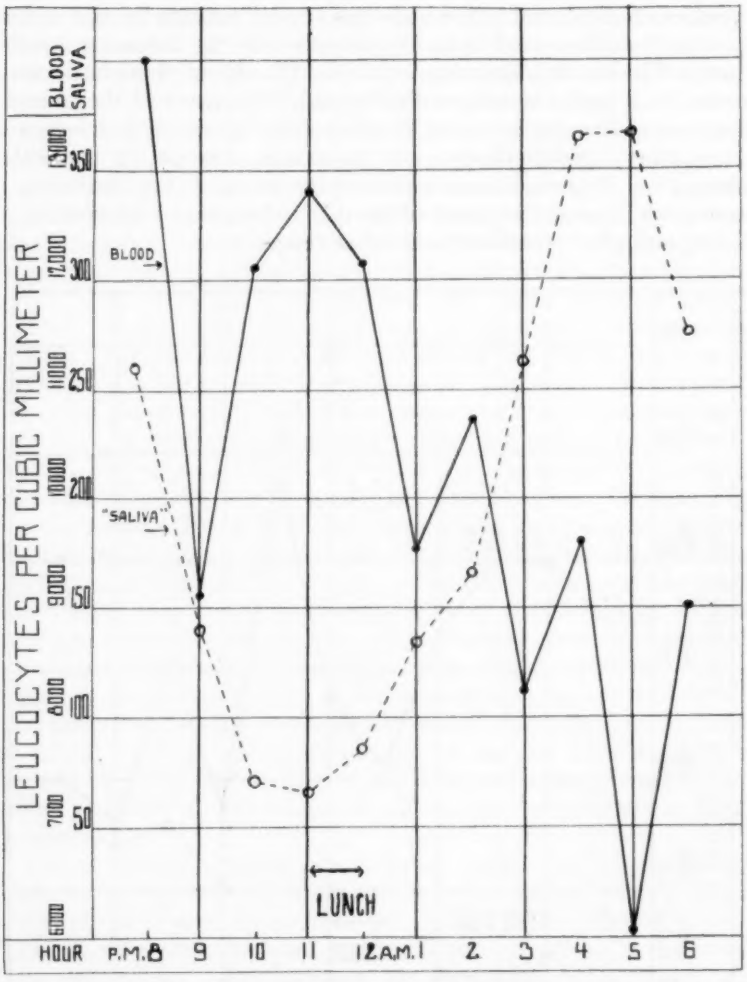

CHART II.—Variations in the number of white blood corpuscles in the blood and saliva of a normal woman during the course of eleven hours.

pointed out most recently by Boldyreff,[11] Sabin, Cunningham, Doan and Kindwall[10] and others, is well shown. The number of saliva leukocytes likewise show a variation, but the general trend is in the opposite direction to the number in the blood at a given time. Normal individuals with a rather high blood leukocyte

count tend to have a higher maximum for the leukocytes in their saliva than those with lower blood counts who tend to have a lower maximum. However, there is a tendency for the salivary leukocyte count to reach its highest point when the blood leukocyte count is lowest, increasing as the blood count falls. The data suggest that there is a constant elimination of leukocytes through the mucous membranes, in this case of the mouth, and that when the leukocyte count of the blood decreases in its daily physiologic fluctuations, the cells find their way rapidly into the saliva and quite possibly into other parts of the gastrointestinal tract.

In the cases charted and from numerous studies of 7 other healthy individuals, the variations from hour to hour during the course of the day or during the course of the night (Charts I and II) are from 5 or less to about 150 per cubic millimeter. One apparently normal individual reached a maximum of 450 per cubic millimeter on one occasion. Such observations were rare. As the pure saliva, obtained by catheterization of the ducts contained practically no leukocytes, the question of their point of origin or supply was investigated. To determine the source of the leukocytes the mouth was washed several times, with water in some experiments, and with physiologic salt solution or diluted sodium bicarbonate in others, and then wiped dry. For additional observations the untreated mucous membrane was studied. Cover glasses were then placed over various parts of the mucous membrane for from thirty seconds to several minutes in such a way as to avoid the saliva. Living leukocytes appeared on the cover glasses, suggesting that they had wandered through the mucosa and reached the exterior in that way. Leukopedesis was most active on both sides of the tongue posteriorly, the buccal surface of the cheeks, the posterior half of the upper surface of the tongue and less active in the anterior half of the upper and lower surfaces of the tongue and the floor of the mouth anteriorly. In these latter places most of the leukocytes were dead, while in the former locations the majority were living.

There was no distinctly characteristic variation for those individuals working during the day in contrast to those working at night. A general tendency, however, for the cell count of the saliva to increase as the working period progressed was frequently noted. No apparent correlation between the amount or consistency of the saliva and the leukocyte number was evident. In each examination the number of squamous epithelial cells per cubic millimeter was determined, but it was found that their number varied independently of the leukocyte number in each specimen. While some contained many epithelial cells and few leukocytes, others showed the reverse condition or increases or decreases in both. A thick stringy saliva was found to have many or few cells, and the same was true of the watery specimens. Chewing gum or tobacco or smoking likewise appeared to influence but little the cell count of

the freshly accumulated saliva obtained by the technique described in the early part of the paper. This is probably because the count depends upon the rate of leukopedesis through the mucous membranes, and the saliva fluid itself is a secondary factor. It is practically the number of leukocytes which 1 (more or less) c.mm. of saliva will wash together in a fairly uniform time from the mucous membranes. Pyorrhea and badly infected gums did not influence the count directly, because the saliva was gathered from inside the mouth, and was freshly accumulated, and had not come into contact with the gum margins. High counts were just as often obtained from toothless persons with smooth, perfectly healed gums as from those with many teeth, or with pyorrhea. Apparently, the predominant white blood cell involved in pyorrhea, at least until the late stages, is the lymphocyte (Beckwith, Simonton and Williams[2]), whereas the predominant salivary leukocyte is usually, with some exceptions, the polymorphonuclear cell, even in lymphatic leukemia.

The greater number of the polymorphonuclear leukocytes of the saliva were adult forms, and probably old, judging from the number of lobes in the nuclei. In disease, however, this was not always true, especially in myelogenous leukemia, discussed later. Red blood cells were not normally present, and when found, always indicated bleeding. It was thought that red blood cells may find their way into the saliva by diapedesis, but because of the nature of the liquid be hemolyzed rapidly. However, there was no evidence to indicate this. Red blood cells may retain their identity for considerable periods of time in the saliva, and none were found on cover glasses placed on the intact mucous membranes and then examined at once.

The variation of the saliva cell count after meals differed in different individuals. When there was a "digestive leukocytosis" in the blood stream there was a decrease in the number of leukocytes in the saliva, but when the leukocytosis did not appear there was a rise in the number of leukocytes in the saliva. Frequently, a rise in the number of leukocytes in the saliva preceded a rise in the number of those in the blood stream. This throws a new light on the "hemoclasic crisis or shock" of Widal. Each case must be examined to determine whether there is really no increase in the number of leukocytes or whether there is an actual increase which is, however, not apparent from the blood count because of the rapid elimination.

When the cells were abundant in the saliva the majority (70 to 99 per cent) were living, but when the cells were few a greater percentage appeared dead. The living cells were rounded and showed actively dancing granules, and the nuclei did not take up the supravital stains until some time had elapsed. It was possible to study the death process in the cells under the microscope. The first

change noted was a cessation of the granular movement in the cells, especially well noted in the polymorphonuclear neutrophils. Then the cells became somewhat more opaque, and increased in size, apparently from the absorption of water. These water-logged cells were the ones which were so easily crushed when attempts were made to draw out films, using the technique followed in making blood smears. The nuclei tend to become round, and the lobes of the polymorphonuclear leukocytes may appear as one, two, three or more spheres. With the swelling, clear areas appear, which are either accumulations of fluid or, as Hirschfeld and Hittmair[12] picture for cells in the blood, areas in which the cytoplasm has retracted from the cell surface. The nucleus later begins to take up the stains and granular motion starts again; this time the granules are usually finer in structure than originally, but they may be of the coarser type seen in the living cell. The process is essentially one of "rigor mortis" of the individual leukocyte, with cloudy swelling, followed by reliquefaction and later disintegration. The stages of death of the polymorphonuclear leukocyte in the saliva are suggestive of a reversal of the process which must take place when a myelocyte matures into the adult leukocyte. The myelocyte appears to lose fluid, the nucleus shrinks and the chromatin is narrowed into a more compact mass, with the formation of the nuclear lobes. The cell itself decreases in size and the granulation becomes more distinct. The dying polymorphonuclear leukocyte, on the other hand, becomes larger, the granules less distinct, the nucleus becomes rounded, with the loss of some or all of the lobulations. The similarity is so marked that it is confirmatory, if confirmation is needed, of the developmental relationship between the two.

It is rather surprising that the leukocytes should continue to "live" for some time (one to two hours at room temperature and two to four hours on a warm stage) in the medium, like the saliva, which differs so much from the blood. The changes which do follow, as the cells begin to die, make it rather difficult to name the individual leukocytes, or at least give them their proper group classification. To aid in identification, leukocytes obtained from blood that was centrifuged were mixed with saliva of an individual, and the changes in the appearance studied. The course of the alterations in the cells was found to be exactly the same as in the saliva itself, and the criteria, such as size, granule activity, staining qualities, were established for the identification of each type of cell. It was found that when sudden increases in the number in the saliva occurred the predominating cell was the polymorphonuclear leukocyte, while when the number of the white cells in the saliva was low the lymphocytes appeared relatively less infrequent. This observation suggests a possible fate of the "showers" of polymorphonuclear leukocytes lost from the peripheral blood stream, described by Sabin, Cunningham and Doane and Kindwall,[10] and

which are the cells that are significant in the fluctuations of the normal white blood cell count. So far no striking differences have been correlated with age or sex.

Leukocytes in the Saliva in Disease. Although the daily variations in the number of leukocytes in the saliva during health are marked within certain limits, in disease the variation may be even more emphasized. In chronic myelogenous leukemia the count is usually much elevated above normal when the white blood cell count is high. However, in a given patient the count of the cells of the saliva may be comparatively lower when the count of the nucleated cells of the blood is 100,000 or 200,000 per cubic millimeter than when it is 45,000 or 50,000 per cubic millimeter. Thus, a patient with 216,000 to 250,000 white cells per cubic millimeter of blood showed a count over several days in the saliva of 221 to 290 per cubic millimeter, while during a period in which the blood leukocyte count varied around 45,000 to 50,000 the salivary leukocytes were from 3900 to 4700 per cubic millimeter. During the course of the day, however, the "reciprocal" relationship between the number of white cells in the saliva and those in the blood still held as in normals. It appears that the white blood cell count in some cases of chronic myelogenous leukemia tends to remain but moderately elevated as long as the leukocyte elimination is active, but when this is decreased the blood leukocyte count may rise to much higher levels. Thus, even if the leukocyte count is comparatively low the disease process may be very active, as shown by the increased production of cells, which are eliminated rapidly through the mucous membrane of the mouth, and possibly other parts of the gastrointestinal tract.

TABLE I.—LEUKOCYTES IN BLOOD AND SALIVA IN CHRONIC MYELOGENOUS LEUKEMIA.

(Man, aged fifty-four years.)

Day.	Time,	Leukocytes per c.mm.	
		Blood.	Saliva.
1	9.45 A.M.	49,000	4200
	10.45	98,000	2800
	11.45	53,000	4100
	12.45 P.M.	110,000	430
	1.45	135,000	350
	2.45	90,000	1150
2	...	51,000	3925
3	...	48,000	4710
4	...	98,000	2100
5	...	49,000	4153
6	...	74,000	534
7	...	154,000	221

Table I shows the variation in the leukocyte count of the blood and saliva of a patient with chronic myelogenous leukemia during

the course of a day and through several days when no Roentgen ray treatment was given. Chart III shows the variation with treatment by short-wave length Roentgen rays. During the twenty-four hours after Roentgen ray treatment of patients with malignant disease there may be a transient rise in the number of leukocytes in the peripheral circulation (Aubertin and Beaujard[13]). This may continue in some cases during the next seventy-two hours (Minot and Spurling[14]), but in most cases a subsequent decrease in

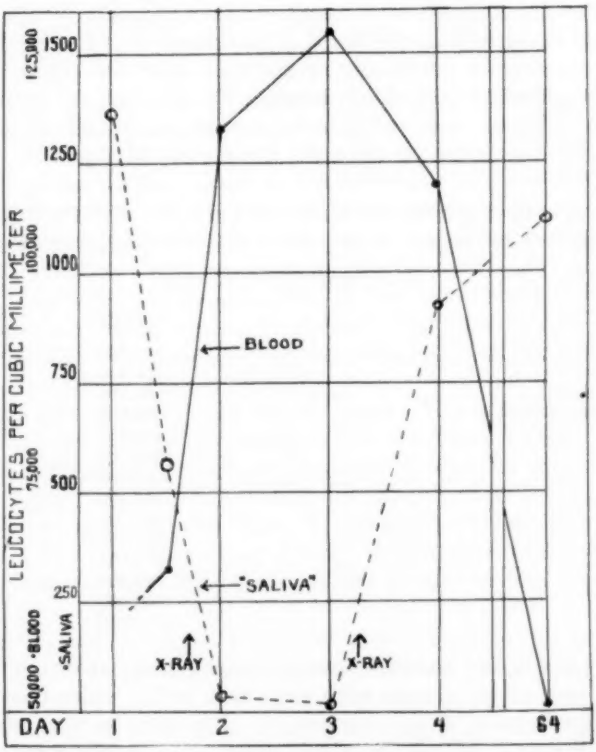

CHART III.—Variation in the number of white blood corpuscles in the blood and saliva after Roentgen ray irradiation over the splenic region of a patient with chronic myelogenous leukemia.

number develops, and at times a definite leukopenia. During the course of the first twenty-four hours after treatment there may be a decrease in number of the leukocytes in the saliva with the temporary increase in number of those in the blood (Chart III). The increase in number of leukocytes in the blood stream during the twenty-four hours after Roentgen ray irradiation is due in part at least to decreased elimination. The presence of myelocytes in the saliva suggests that these immature cells do not mature in the

blood stream when they have reached it under pathologic conditions, but are eliminated as such. The maturation process under normal conditions probably takes place in the bone marrow. With the decrease in the number of leukocytes in the blood there is a great increase in the number in the saliva during two to five days following Roentgen ray therapy. In some cases the cells have been too numerous to count without dilution of the saliva, the material resembling pus in its appearance.

In the myeloid form of leukemia with many myeloblasts in the blood Roentgen ray therapy may not influence markedly the number of white blood cells in the blood or in the saliva. Evidently, these very immature or pathologic myeloblasts have but limited powers of leukopedesis, which may account for the lack of response to therapy. Three cases of this type were examined with similar findings. The following data are illustrative of this:

TABLE II.—LEUKOCYTES IN BLOOD AND SALIVA IN CHRONIC MYELOGENOUS LEUKEMIA, ONE AND A HALF YEARS' DURATION.

(Man, aged forty-four years.)

Day.	Leukocytes in blood.	Leukocytes in saliva.
1	281,400	45
2	268,300	2620
3 (A.M.)	399,000	2330
3 (P.M.)	502,000	520
4	305,000	100
6	386,000	2667
8	442,000	1890
9	492,000	880
10	248,000	935
11	235,000	3152
14	171,000	822
15	329,000	2278
23	166,000	93
28	731,000	783

The patient had received several Roentgen ray treatments in the earlier part of his disease with reduction of his white blood count and improvement in his symptoms. The data in the table were taken during a relapse in which many of the cells were of very immature type (atypical myeloblasts) in contrast to the more mature forms (myelocytes) which appeared in the blood in the earlier part of his disease.

During this period the patient received 3000 electrostatic unit seconds of short-wave length Roentgen rays in thirteen divided doses. The myeloblasts in the blood varied from 32 to 62 per cent, and the adult polymorphonuclear cells made up but a small percentage of the remainder.

When the myelocytes were numerous in the blood their number was also increased in the saliva. This parallel relationship, however, did not hold in all diseases. In chronic lymphatic leukemia,

although the lymphocytes in the saliva were more numerous than normal, the polymorphonuclear leukocytes appeared in greater proportion than in the blood. The following table is illustrative of this point, and represents one of many similar observations.

TABLE III.—LEUKOCYTES IN BLOOD AND SALIVA IN CHRONIC LYMPHATIC LEUKEMIA.

	Number, per c.mm.	Polymorphonuclear leukocytes, per cent.	Lymphoid and mononuclear leukocytes, per cent.
Leukocytes in saliva	386	86.0	14.0
Leukocytes in blood	19,000	32.5	67.5

It is very probably, as Bunting and Huston[4] have shown, that the bulk of the lymphocytes leave the body through the lower portions of the gastrointestinal tract, so that the excretion from the mucous membranes of the mouth represent but part of the process. Observations on a patient with chronic lymphatic leukemia and an intestinal fistula showed, during an aleukemic phase, a leukocyte count of 9500 per cubic millimeter, in his peripheral circulation, 1850 per cubic millimeter in the clear fistula fluid, and 555 per cubic millimeter in the saliva. The white blood cells in the fistula fluid were mostly lymphocytes, while in the saliva the polymorphonuclear cells constituted 66 per cent and the lymphocytes and mononuclear cells 34 per cent. The lymphocytes constituted 59 per cent of the leukocytes of the blood at that time.

In the "aleukemic" form of lymphatic leukemia, and in some related types of lymphoblastoma (with lymphomatous invasion of the bone marrow) the condition in the saliva is very interesting, because it has been found that it may contain more leukocytes per cubic millimeter than the blood. Table IV shows this relation:

TABLE IV.—LEUKOCYTES IN BLOOD AND SALIVA IN ALEUKEMIC LEUKEMIA AND RELATED CONDITIONS.

Patient No.	Leukocytes in blood, per c.mm.	Leukocytes in saliva, per c.mm.
1	8250	8,490
2	3300	13,900
3	2200	6,320
4	3925	3,185
5	4000	12,500

In lymphoblastoma of the Hodgkin's type there was frequently a rather large number of cells in the saliva. In one patient the number of leukocytes in the blood was 6200 per cubic millimeter, while in the saliva repeated counts showed from 7000 to 8000. An occasional patient with Hodgkin's disease was encountered with a great excess (90 per cent) of polymorphonuclear eosinophil cells in the saliva, entirely out of proportion to those in the blood (1 to 2

per cent). A curious feature is that this condition may be present on some days and absent on others. This is of interest in view of the increased number of eosinophil cells frequently present in the enlarged lymph nodes and sometimes seen in large numbers in the blood stream.

When the bulk of the circulating leukocytes are lymphocytes it is not always possible to correlate the salivary cell count with that of the blood, because of the excretion from less accessible parts of the mucous membranes of the alimentary tract. The reduction in the rate of production of the lymphocytes is frequently seen in the saliva in the simultaneous reduction of the output, as shown in Table V.

TABLE V.—LEUKOCYTES IN BLOOD AND SALIVA IN LYMPHOBLASTOMA (ALEUKEMIC LYMPHATIC LEUKEMIA TYPE).

(Man, aged thirty-five years.)

Day.	Leukocytes in blood, per c.mm.	Leukocytes in saliva, per c.mm.
1	2200	6320
1 (Roentgen ray treatment over spleen)		
2 (Roentgen ray treatment over spleen)		
2	1400	3290
3	1900	830
4	2150	1560

In this patient there were 28 to 30 per cent polymorphonuclear netrophils in the blood, and from 75 to 90 per cent in the saliva.

These observations throw a new light on the aleukemic type of lymphatic leukemia. There is apparently a rapid elimination of the lymphocytes which are being produced in increased numbers in the hyperplastic lymphoid tissues of the body. Irradiation of such a patient, if he has a leukopenia, with the Roentgen rays frequently reduces the amount of metaplastic lymphoid growth in the bone marrow and the myeloid elements increase in number in the peripheral circulation, with a resulting increase in the peripheral blood count. This is in contrast to the effect of Roentgen ray or radium irradiation of a patient who has leukopenia because his bone marrow is nonproductive or aplastic. In that case a more profound leukopenia develops. This point proved of practical value in the irradiation of other types of patients with leukopenia. If the leukocyte count in the peripheral circulation was low and the excretion rate in the saliva was definitely high the bone marrow was not aplastic and the patient could be irradiated with safety. The effect of the Roentgen ray treatment of such a patient who had a leukopenia because of rapid elimination of the leukocytes (in contrast to one whose leukocyte *production* was low) is shown in Table VI:

TABLE VI.—LEUKOCYTES IN BLOOD AND SALIVA IN CARCINOMA OF BREAST.

(Woman, aged sixty-seven years.)

Day.	Blood.	Saliva.
1	4270	6040
2 (A.M.) (Roentgen ray treatment over breast)		
2 (P.M.)	7200	3895
87	18,430	9200

Formerly one would have hesitated to treat such a patient because of the fear of producing a further destruction of an aplastic bone marrow.

In a patient with a clinically aplastic anemia the white cell count was 850 per cubic millimeter of blood, while the saliva showed, on repeated examinations 1 or no leukocytes per cubic millimeter. In contrast to this another case had a white blood corpuscle count around 700 per cubic millimeter for weeks, while the saliva cell count was around 120 per cubic millimeter during this time. Autopsy showed miliary tuberculosis, but the marrow was not fatty and aplastic, accounting for the comparatively high output when the blood count was so low.

In a number of cases of carcinoma of the breast the leukocyte count in the saliva was higher than would be expected from the blood count. The hourly variations in 4 cases are shown in Table VII. A fifth case had a blood leukocyte count of 5000 per cubic millimeter and a saliva leukocyte count of 6040.

TABLE VII.—LEUKOCYTES IN BLOOD AND SALIVA IN CARCINOMA OF THE BREAST.

	Case I.		Case II.		Case III.		Case IV.	
	Blood.*	Saliva.*	Blood.	Saliva.	Blood.	Saliva.	Blood.	Saliva.
9.00 A.M.	7200	500	8400	8000	10,000	8000	8,200	7600
10.00	6600	1000	8000	8200	8,600	8000	9,600	4800
11.00	8400	520	9000	7700	6,400	8200	8,800	8000
12.00	6800	580	9400	2300	8,000	8400	15,000	1600
2.00 P.M.	6400	2850	8000	9600	12,000	7000	8,200	7600
3.00	7800	1600	6600	9600	7,000	4200	8,000	7800
4.00	6000	4800	7000	9200	8,600	550	9,400	6000

* Figures show number of leukocytes per cubic millimeter.

The number of white blood corpuscles in the blood and saliva of 2 patients with carcinoma of the cervix of the uterus is shown in Table VIII.

In acute rhinitis the cells were very few in number in the saliva (1 to 5), although the blood showed a slight leukocytosis. In other

simple leukocytoses (infections and so forth) the leukocytes in the saliva were comparatively few in proportion to those in the blood. Thus a patient with pyelitis had a leukocyte count of 14,500 per cubic millimeter of blood, but only 52 per cubic millimeter in the saliva.

TABLE VIII.—LEUKOCYTES IN BLOOD AND SALIVA IN CARCINOMA OF THE CERVIX.

	Case I.		Case II.	
	Blood.	Saliva.	Blood.	Saliva.
9.00 A.M.	5200	520	8,400	
10.00	4800	580	12,000	
11.00	4600	580	8,400	
12.00	4400	1000	9,200	Cells scanty, 25 or less.
2.00 P.M.	5400	0	8,400	
3.00	5200	0	8,000	
4.00	6400	2000	8,000	

Of 2 patients with pernicious anemia, 1 showed a high leukocyte output in the saliva and 1 was low. Of the other patients examined, including various forms of cutaneous cancer, endothelioma, mixed parotid tumor, the leukocyte counts of the blood and saliva were within normal limits.

General Discussion. The data suggest the close relationship between the supply of leukocytes in the blood stream and the leukocytes which appear in the saliva. In health there appears to be a reciprocal relationship, in which the leukocytes are fewer in the saliva when they are more numerous in the blood, up to a certain point, when increased elimination raises the number in the saliva, with a decrease in the number in the blood. The nature of the regulatory mechanism has not been determined. It is certainly disturbed in disease so that there occur conditions with relatively few white blood cells in the saliva with great increases in the blood as at times in chronic myelogenous leukemia and others in which there is a manifest leukopenia in the blood, but great numbers of leukocytes in the saliva, as in aleukemic leukemia and in the late stages of Hodgkin's disease. It suggests that we may classify leukocytosis and leukopenia according to the working of the regulatory mechanism.

Leukocytosis: (*a*) Increased production of leukocytes (pathologic); (*b*) decreased elimination (pathologic and physiologic).

Leukopenia: (*a*) Decreased production of leukocytes (pathologic); (*b*) increased elimination (pathologic and physiologic).

In the curves presented the reciprocal relation of the number of leukocytes in the blood and in the saliva is not always clear cut, because sudden changes in the blood count may start in the interval between the times when the counts were taken, so that sometimes one is viewing the middle of an increase or decrease in the number of leukocytes and not the beginning of the process. This is well

shown when the counts are taken as close together as possible—ten-minute intervals—when the agreement is very close. At times also the cells may be eliminated in greater proportion at other points in the gastrointestinal mucous membranes. Frequently a change in the differential count suggests a loss of polymorphonuclear leukocytes, and at other times there may be an actual decrease in the number of lymphocytes. The latter, however, tend to keep at a more uniform level than the former.

The "digestive leukocytosis" which, as many authors have noted, may not be present, can be perhaps linked up with the rate of elimination of the leukocytes. The increase of the lymphocytes in the saliva after meals, when the blood fails to show a "digestive leukocytosis," has been noted repeatedly in this study. It would be interesting to see if both the increase in the blood or the increase in the saliva are absent in disease of the liver, or whether the "hemoclasic crisis or shock of Widal" is only apparent.

As to the function of the cells in the saliva or their ultimate disposition, little can be said. It can be surmised that the adult polymorphonuclear neutrophils and some of the mononuclear cells may function as phagocytic agents during the short time that they are in the mouth. This, however, is doubtful. This function probably does not account for the presence of immature myelocytes and lymphocytes. The number of cells eliminated per day must be considerable, but there are, of course, other points of destruction or elimination of the leukocytes. The increase in products of leukocytic decomposition after Roentgen ray treatment in myelogenous leukemia shows that a considerable number of cells must die in the body itself, unless one surmises that the products are resorbed from the decomposition of the leukocytes in the lumen of the stomach or intestines.

The appreciation of the general significance of the numerical relations of the leukocytes in the saliva, together with the method of enumerating them, opens possibilities for further studies. The behavior in each disease remains to be investigated, and the effects of various therapeutic methods and drugs may be tested. The effect of agents which will increase the salivary leukocytes and those which will decrease them may be studied both to discover the mechanism which controls the "leukocyte level" of the body as well as to note the clinical effects where such agents are indicated.

Summary and Conclusions. 1. The present work is a quantitative and qualitative study of the leukocytes which appear in the saliva in health and certain diseases.

2. The saliva, as it appears at the opening of the ducts, is practically free from leukocytes. The white cells are washed together from the mucous membranes, through which they have wandered.

3. The average leukocyte count in the mixed saliva (in health) varies from 5 to 150 (rarely as high as 450) cells per cubic millimeter,

the variations appearing during the course of the day, sometimes quite rapidly.

4. The variations in the number of the leukocytes in the saliva accompanies the changes in the number of leukocytes in the blood, but the relation is most commonly a reciprocal one.

5. When a "digestive leukocytosis" fails to show in the blood it is sometimes evident in a great increase in the number of cells in the saliva.

6. All types of white blood corpuscles, and probably blood platelets are found in the saliva, the number varying with the disease.

7. Although the percentage of polymorphonuclear leukocytes bears much the same relation to the other cells in the normal saliva as in the blood, it may be comparatively increased in chronic lymphatic leukemia and similar diseases.

8. When the cells are abundant in the saliva the majority are living, but when they are scanty a greater proportion may show no signs of life.

9. The process of "rigor mortis" of polymorphonuclear leukocytes is described. Some of its stages are suggestive of a reversal of the process of maturation of the myelocytes.

10. The number of leukocytes in the saliva is greatly increased in chronic myelogenous leukemia, often more so when the count is moderate than when it is extremely high. After Roentgen ray treatment there appears to be a great elimination of leukocytes, most of them living, in the saliva.

11. The presence of myelocytes and young polymorphonuclear leukocytes in the saliva suggests that when immature cells enter the blood stream they are eliminated as such, and do not mature in the peripheral circulation.

12. The cells may be greatly increased in number in the saliva in lymphoblastoma. In aleukemic lymphatic leukemia the number of leukocytes per cubic millimeter of the saliva may be greater than that of the blood, the low white blood cell count being associated with the increased rate of elimination. In Hodgkin's disease the elimination of lymphocytes and eosinophils in the saliva may be marked.

13. When leukopenia is accompanied by increased elimination of leukocytes in the saliva, cell production is active, and Roentgen ray irradiation of lesions in the body is not contraindicated.

14. It appears that we may have leukocytosis from increased production of leukocytes or from decreased elimination and leukopenia from decreased production or from increased elimination.

15. The mucous membranes of the mouth, and probably other parts of the gastrointestinal tract act as points of elimination of leukocytes, in the general regulatory mechanism which tends to keep the blood elements within certain numerical limits.

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COARCTATION OF THE AORTA WITH STAPHYLOCOCCUS ALBUS ENDOCARDITIS.

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That portion of the aorta which lies between the left subclavian artery and the point where the ductus arteriosus joins the under side of the arch of the aorta is known as the isthmus. It has acquired this name from the fact that during fetal life this part of the aorta is used very little and at birth is generally found to be of smaller caliber than the aorta proximal and distal to it. Normally this narrowing disappears soon after birth except, according to Thérémin,[1] in about 6 per cent of individuals in whom a slight constriction of the isthmus persists. Unless the constriction amounts to more than 2 mm. Thérémin does not consider it abnormal. When it is greater than 2 mm. the condition is classed as a cardiac anomaly and is known as *coarctation of the aorta* or *stenosis of the*

isthmus. It is one of the well-recognized forms of congenital cardiac disease and is often accompanied by a distinctive symptomatology.

That hearts with congenital anomalies are peculiarly susceptible to infectious processes is a fact which emerges in a striking way from numerous statistical studies (Abbott[2,3]). Microörganisms of many kinds have been found to be the causative agents in the bacterial processes observed in these anomalous hearts. The rarity of Staphylococcus albus as the pathogenic organism in such conditions, as well as in bacterial endocarditis without congenital cardiac disease has prompted the following report of a case of coarctation of the aorta with Staphylococcus albus endocarditis and endarteritis.

Case Report.—O. N., age five years.

Present Illness. Patient was in good health until five days before admission. The onset was sudden, with headache, fever and restless irritability. Two days after the onset he developed a generalized erythematous rash resembling a scarlet fever eruption. Throat was not inflamed, and blanching test with Dochez antitoxin was negative. The rash persisted two days. The child was constantly restless and irritable and complained of pain in the legs. Temperature before admission was between 102° and 104°. Bowels were constipated.

Past History. Normal birth. Patient has seemed a bright, robust child. Otitis media at eight months; this cleared up quickly. One month before admission he was ill three days with vomiting and malaise but no fever.

Family History. Mother and father living and well. No other children.

Physical Examination. The patient is a pale, sick, irritable, restless child, lying on his side with thighs and legs flexed and resisting efforts to straighten them. Eyes and ears are normal. Tonsils moderately large; not inflamed. No signs of cranial nerve lesions. Neck and spine flex normally. Heart is regular and rapid; not enlarged. Over the whole precordium there is a loud blowing systolic murmur which may be heard with less intensity over the entire chest, front and back. This murmur is peculiar in that it gives one the impression of coming from somewhere else than the heart. It is, nevertheless, quite synchronous with the first heart sound, which can be distinctly heard despite the murmur. No thrill. The lungs are clear, except for a few fine moist râles at the left base. The abdomen is distended; no viscera felt. Superficial lymph nodes: A few small glands are palpable in the posterior cervical chains. Extremities: Over both feet, but more numerous on the left, there are irregular hemorrhagic spots 2 to 10 mm. in diameter. A few of these have pale, slightly yellow and elevated centers. Two of the toes of the left foot are deep blue at the tip. both feet are tender and especially so over the small pustular spots.

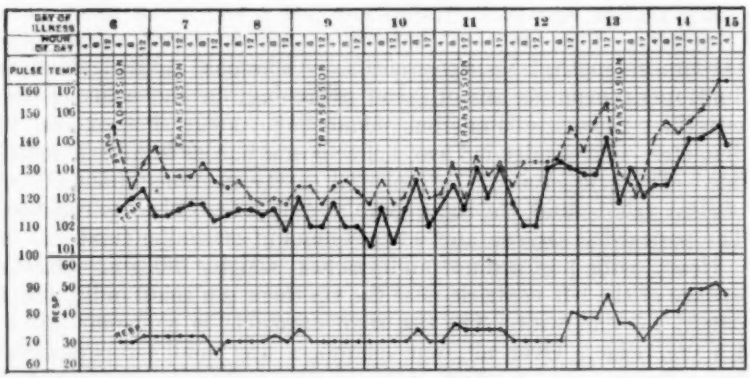
The dorsum of each foot is edematous; pulsation in the dorsalis pedis arteries is barely perceptible. Deep reflexes are active. No Babinski, Brudzinski or Kernig. Abdominal reflexes present. Pulse is regular and soft. Blood pressure, 128 systolic and 78 diastolic.

Blood Count. Erythrocytes, 3,250,000; hemoglobin, 85 per cent (Sahli); leukocytes, 15,600; neutrophils, 73 per cent; lymphocytes, 24 per cent; transitionals, 3 per cent.

Lumbar Puncture. Spinal fluid clear; no increase of pressure; cells, 12; lymphocytes, 90 per cent; globulin, ±.

Wassermann test, negative. Widal test, negative. Urine: Specific gravity, 1006 to 1016. Albumin, 0. Glucose, 0. Microscopic: A few leukocytes.

Roentgen ray of the chest showed a rather large left hilum shadow, but no definite evidence of consolidation. Roentgen ray of thighs and legs showed nothing abnormal. Roentgen ray of feet showed a little fuzziness of the internal cuneiform of the left foot. Blood culture contained a nonhemolytic Staphylococcus albus.



Course in the Hospital. The patient lived nine days after admission to hospital. The pulse, temperature and respiration records are shown in the chart.

The local signs and Roentgen ray suggested a suppurative focus in the left foot; an incision under chloroform anesthesia was made. No focus was found but cultures from the tissues also grew out a Staphylococcus albus. The child became more and more toxic; the spleen and liver became palpable, the edge of the latter extending 8 cm. below the costal border in the midclavicular line. On the legs and buttocks fresh petechial spots appeared; some of them had tiny pustular centers. During the last two days numerous fresh petechiæ were noted on face, chest and abdomen. There were also a few dusky erythematous spots fading on pressure and

slightly elevated. These measured 0.5 to 1 cm. in diameter. Two days before death the child was intermittently stuporous; he lay on his side with knees drawn up; the neck could be flexed until the chin touched the sternum, but this caused discomfort. The Kernig sign was positive. A to-and-fro friction rub was heard in the second and third left interspaces near the sternum. The loud blowing systolic murmur persisted, but did not change perceptibly in quality or intensity. Immediately after a transfusion the murmur was inaudible for a few hours.

A blood count the second day after admission, twenty-four hours after a transfusion of 200 cc. of father's blood: Erythrocytes, 4,720,000; hemoglobin, 78 per cent; leukocytes, 16,100; neutrophils, 80 per cent; lymphocytes, 19 per cent. Six blood cultures were taken and each showed a nonhemolytic Staphylococcus albus.

The child was given intravenous injections of gentian violet (5 mg. per kilo of body weight) and four transfusions with the father as donor. Neither the course of the disease nor the condition of the patient was perceptibly affected by treatment, and nine days after admission he died in coma.

Autopsy, by Dr. B. H. Paige, one and a half hours after death (abstract): The body is that of a well-developed white boy, 111 cm. in length. No *rigor mortis*. Abdominal cavity: No free fluid; peritoneum is smooth and glistening; in the walls of the intestines there are numerous hemorrhagic areas, 1 to 2 cm. in diameter. Liver edge is 7 cm. below costal border in midclavicular line. Thoracic cavity: Left pleural cavity contains about 50 cc. of clear yellow fluid, the right contains only a few cubic centimeters. The pericardial sac contains a small amount of similar fluid.

Heart, with pericardium and trachea, weighs 190 gm. On the surface of the left ventricle near the tip there is a small milky white patch, 1.5 cm. wide. On the right ventricle is a similar patch, 1.5 cm. wide. Over all four chambers are small subpericardial hemorrhages, one of which shows a pale yellowish center with a hemorrhagic peripheral zone. The myocardium is deep red in color, with a tawny yellow area irregular in outline and about 1 cm. in its greatest diameter on the posterior wall of the left ventricle. The walls of this ventricle are hypertrophied and in them are small abscesses. The ventricular cavity is dilated and the septum appears mottled. In the endocardium of the right auricle is a small reddish-gray granular area, 3 to 4 mm. in diameter. The endocardium of the right ventricle contains tiny petechiæ and in the anterior papillary muscle is a deep red area with a tiny yellow center. The foramen ovale is closed. In the endocardium of the left ventricle are petechiæ also, one on the posterior papillary muscle being conspicuous. The leaflets of the tricuspid, pulmonary and mitral valves are negative and the chordæ tendinæ are not thickened.

On the aortic valve, hanging from the ventricular surfaces of the

anterior and left posterior leaflets, is a large reddish-gray, friable vegetation, which completely fills the aortic ring. Below this, on the ventricular wall are two small abscesses. On the right posterior leaflet is a slight roughening of the surface. Between the anterior and left posterior leaflets, at their point of attachment, is a fenestration. The heart measurements are: Right ventricular wall, 4.5 cm.; left ventricular wall, 11 cm.; length of left ventricle, measuring from right side of anterior cusp attachment to the tip of the ventricle externally, 5.7 cm.

The origin of the left coronary artery is above the points of highest attachment of the valve leaflets and the opening of the right coronary is large.

Pulmonary artery: In the wall of the pulmonary artery, a short distance above the valve, is a small red, elevated nodule, 1 mm. in diameter, having a yellow center. The site of the pulmonary opening of the ductus arteriosus is visible, but it is not patent.

Aorta: In the region of the sinuses of Valsalva are tiny areas appearing brighter yellow than the remainder of the vessel wall. At the isthmus the aortic wall is constricted and a thin fold projects into the lumen, leaving a narrow orifice, 3 mm. wide and 4.5 mm. high. In line with it is the closed ductus arteriosus orifice. Beyond the stenotic region the aortic wall dilates again, showing also on its inferior surface, a depression just distal to the coarctation. From the intimal surface, 5 to 10 mm. beyond the constriction, half the inferior surface of the vessel wall is covered by a small, pale, reddish-gray, friable thrombotic mass. A row of tiny accessory openings accompanies the mouths of the costal arteries. On the wall of the left common iliac artery, just below the bifurcation of the aorta, is a thrombotic mass that fills the main portion of the lumen.

MEASUREMENTS.

Circumference of aorta at line of attachment of leaflets of the aortic valve	3.65 cm.
Circumference 1 cm. above line of attachment of the leaflets of the aortic valve	3.50 "
Circumference at level of ductus arteriosus (coarctation)	1.40 "
Circumference 1 cm. distal to ductus arteriosus	3.50 "
Circumference 2 cm. distal to ductus arteriosus	2.90 "
Thickness of aortic wall immediately above attachment of valve leaflets	2.00 mm.
Thickness 1 cm. above valve leaflets	1.50 "

The lungs show numerous subpleural hemorrhages and an anomalous fissuration (right). The spleen weighs 170 gm.; it shows infarcts and small abscesses. The liver weighs 900 gm. Beneath the capsule are scattered small abscesses. In the portal fissure there is a lymph node with hemorrhages and a purulent center. The gall bladder is normal. The pancreas is normal. In the stomach there is a small circumscribed erosion in the gastric mucosa.

Throughout the intestines there are hemorrhagic areas up to 2 cm. in diameter. These lie in the mucosa and extend into the muscle. The kidneys are similar. The left one weighs 100 gm. The surface is mottled and shows many small hemorrhages and pale areas, some of which are yellowish-white. On section the striations appear normal and the Malpighian corpuscles are clearly seen. There are several wedge-shaped infarcts. Scattered through the cortex and medulla there are tiny yellowish circumscribed areas, 0.5 cm. in diameter. Bladder mucosa is dotted with tiny hemorrhages. Adrenals, testes and prostate show nothing noteworthy. Brain and spinal cord not removed.

SUMMARY. A boy, aged five years, with a past history of good health and apparently normal capacity for physical activity, suddenly became ill with headache, fever and restless irritability. During the fourteen days between the onset of his illness and his death there was a high continuous type of temperature.

The clinical data to be emphasized were: (1) Four types of skin lesion: (*a*) A diffuse scarlatiniform eruption, appearing two days after the onset and persisting for two days; (*b*) hemorrhagic spots first noted on the fifth day of his illness; these continued to appear during the nine days he was under observation and they varied from 2 to 10 mm. in diameter and were most numerous on the feet, legs and buttocks; (*c*) a few hemorrhagic spots with small pustular centers; (*d*) slightly elevated dusky erythematous spots fading on pressure and measuring 0.5 to 1 mm. in diameter. (2) The presence in the blood on each of six cultures of a nonhemolytic Staphylococcus albus. (3) The absence of any detectable portal of entry or primary focus. (4) A heart of normal size without the physical signs of any of the common valvular lesions. (5) A loud blowing systolic murmur heard not only over the precordium but over the entire chest front and back; although loud and lasting throughout most of the systole, this murmur did not obliterate the first heart sound; following a transfusion it temporarily disappeared. (6) Almost imperceptible pulse in dorsalis pedis arteries. (7) No collateral arterial circulation. (8) Enlargement of the liver and spleen.

Autopsy showed: Coarctation of aorta; acute bacterial endocarditis, Staphylococcus albus, aortic valve; acute endarteritis of aorta; abscesses of heart, intestine, spleen, pancreas and left foot; infarcts of kidney and spleen; mycotic aneurysm of iliac artery; subcutaneous, conjunctival, subpericardial, subpleural, submucous petechiæ; hydrothorax; edema of lungs; congenital malformation of lung (anomalous fissuration).

Discussion. The following account of the clinical variations, symptomatology, pathogenesis and pathology of coarctation of the aorta (stenosis of the isthmus) has been taken largely from the excellent papers of Bonnet,[4] Barié[5] and Abbott.[2]

Coarctation of the aorta may remain entirely latent throughout life and be discovered unexpectedly at autopsy. Such individuals have often been vigorous and entirely free from symptoms of cardiac insufficiency. Or, coarctation may be quite latent during many years of active life and symptoms occur first as a result of an additional heart injury, such as endocarditis, or from overtaxing the circulatory apparatus which had long maintained a successful compensatory mechanism. In a small number of cases symptoms referable to the obstruction are present throughout life.

When symptoms occur they may be quite similar to those of other forms of cardiac insufficiency; the intense cyanosis often seen in other types of cardiac anomalies is, however, quite rare. In a few of the reported cases the symptoms have been more specifically related to the lesion and to the unequal circulation in the upper and lower parts of the body which results from it—violent pulsations in the vessels of the head and neck, buzzing in the ears, headaches, lividity of the face, suffusion of the head and neck, epistaxis and hemoptysis. But when the diagnosis can be made it is largely dependent upon the physical signs. These may show a curious lack of parallelism with the degree of constriction and with the symptoms. The cases uncomplicated by other anomalies and valvular lesions afford the most suitable subjects for a study of the signs peculiar to the lesion. From a review of such cases, Abbott[2] and Bonnet[4] stress the following physical signs: Violent pulsations in the arteries of the upper half of the body, dilated and tortuous vessels occupying the course of the internal mammary arteries on either side of the sternum or the posterior intercostal or scapular arteries behind, a varicose mass of vessels beneath the skin of the abdomen, a network of tortuous pulsating vessels in both supraspintus fossæ; over the course of these dilated collaterals a murmur, systolic or postsystolic, may be heard and sometimes a synchronous thrill is palpable. The radial pulses may be unequal on the two sides. In contrast with the condition of the arterial tree above the waist, the pulsations of the femoral, popliteal, posterior tibial and dorsalis pedis arteries may be imperceptible or weak and retarded. The pulsation of the abdominal aorta also may be imperceptible.

The heart in uncomplicated cases is sometimes enlarged, sometimes of normal size. In many of the reported cases coëxisting cardiac anomalies or valvular lesions might well have caused the enlargement of the heart noted. Abbott states that a precordial thrill was present in only 3 of the 142 cases analyzed by her.

Auscultation may or may not reveal the presence of murmurs over the cardiac area or over the dilated vessels of the collateral circulation. The diastolic murmurs recorded in some of the reported cases have probably in every case been due to associated lesions and not to coarctation. Bonnet states that in 4 of 15 cases, in which the auscultatory signs were noted, there was no audible

murmur. When the coarctation itself produces a murmur it may be produced at the site of the constriction or in the dilated collateral vessels. It is sometimes noted as systolic, sometimes as postsystolic. It may be limited to the cardiac area, and in such cases is apt to be of equal intensity at the base and at the apex; in some cases it has been confined to the area between the left clavicle and the left third rib. Frequently, however, the murmur is heard over a wide area and, as in the subject of this report, is audible with almost uniform intensity over the entire chest, front and back. In the author's case the first heart sound could be distinctly heard despite the fact that the murmur was audible during the systolic phase of the cardiac cycle. The murmur gave one the impression of coming from somewhere outside of the heart. The quality of the murmur is described by different authors as rough, rasping, blowing or soft. Its temporary disappearance after transfusion is in accord with the observations of Etlinger,[6] who described a case of coarctation of the aorta in which a murmur was intermittently present.

PATHOGENESIS. Bonnet has offered the most plausible explanation of the origin of coarctation of the aorta. He pointed out that there are two distinct forms: (1) The infantile; this occurs in the newly born, is probably developmental in origin and consists of a diffuse narrowing of the isthmus; many of the cases of this type have other cardiac anomalies. (2) What he calls the adult type; these are the cases seen for the most part after infancy and never in the fetus nor at birth before the closure of the ductus arteriosus has begun. In this group the coarctation seems to result from an extension of the tissue of the ductus into the wall of the aorta. At the time shortly after birth that the ductus undergoes a process of closure this tissue also contracts. The "adult type" is hence not of developmental origin.

PATHOLOGY. The constriction of the infantile type with diffuse stenosis of the isthmus may vary from complete obliteration of the lumen to a just perceptible narrowing of this portion of the aorta. In this type the narrowing rarely begins abruptly; it generally is found to diminish progressively in caliber to maximal constriction which is maintained for a certain distance. The maximal constriction is between the left subclavian artery and ductus arteriosus. The adult type is characterized by a much more abrupt constriction a little beyond the subclavian artery, as if the aorta had been narrowed by a ligature. Nearly always the constriction is most marked on the convex side of the aorta. The coarctation is always close to the point of insertion of the ductus. Occasionally it is situated at the proximal side of the ductus, sometimes it is at exactly the same level, but most frequently it is at the distal side of the ductus or just below its point of insertion. Immediately beyond the stenosis the aorta in many cases has been found to be

widely dilated; in the case here reported there was a distinct dilatation just beyond the narrowing. The ductus itself was patent in 13 of the 142 cases analyzed by Abbott. For a description of atypical forms the papers of Bonnet should be consulted. Evidence of the collateral circulation is often found in the enlargement of the vessels of the arch, sometimes to twice their normal caliber, and in the occurrence of dilated and tortuous vessels forming the anastomosis. This is accomplished by the superior intercostals, the internal mammaries and the posterior scapular branches of the transversalis coli above, communicating with the first four aortic intercostals, the phrenic and superficial and deep epigastrics below the stenosis. Hypertrophy and dilatation of the heart are usually not found in the infantile type, but are frequent in the adult form. In many of these cases, however, a concomitant valvular disease provides an adequate explanation for the enlargement. Associated abnormalities, such as anomalous semilunar cusps, irregular origin of the vessels from the arch, patency of the foramen ovale or duct, persistent left superior cava, septal defects, transposition of the great trunks, congenital stenosis, are far more common in the infantile than in the adult type.

In the light of these data it is clear that the case here reported corresponds to Bonnet's adult type without associated anomalies and without either enlargement of the heart or macroscopic collateral circulation.

Staphylococcus Albus Endocarditis. Staphylococcus pyogenes aureus is one of the more common organisms associated with acute bacterial endocarditis and sepsis. The clinical features of this condition have been well described by Lenhartz,[7] Jochmann[8] and others and need not be reviewed here. Staphylococcus albus is, however, rare as a cause of bacterial endocarditis and sepsis. Lenhartz states, and the case here reported substantiates his opinion, that Staphylococcus albus may at times cause a highly malignant form of endocarditis and sepsis with the same clinical phenomena and fulminating course so often seen in the Staphylococcus aureus cases. The different types of skin lesion observed in our case, and particularly the small hemorrhagic spots with pustular centers deserve special emphasis. These pustular petechiæ are quite different from the petechiæ with white centers seen in subacute bacterial endocarditis. Though often very small, they are real pustules with a hemorrhagic halo. Only a small proportion of the hemorrhagic lesions show the central pustule; careful search may be necessary to find them. In the writer's experience these lesions have occurred only in Staphylococcus sepsis and apparently serve to differentiate it, by clinical observation alone, from Streptococcus and other forms of sepsis. In our case no detectable effect upon either the bacteremia or the clinical condition was produced by intravenous injection of gentian violet.

THE SPECIAL SUSCEPTIBILITY OF CONGENITALLY MALFORMED HEARTS TO ACUTE AND SUBACUTE ENDOCARDITIS. A discussion of the recorded observations and ideas on this interesting question is beyond the scope of this paper. The existence of such a special susceptibility has been noted by numerous observers and seems now to be an established fact, but as yet no satisfactory explanation has been offered for it. In a recent comprehensive review of the subject Abbott[3] gives an analysis of 555 cases of congenital cardiac disease. She found that 98, or 17.6 per cent, of these hearts had acute or subacute endocarditis. Anomalies of the left heart are more likely to have the subacute form of endocarditis and hearts with anomalies of the right side are more likely to have acute bacterial endocarditis. In Abbott's collected cases there were 46 instances of coarctation, and of these 7 had bacterial lesions. Bahn[9] has recently reported a case with dextrocardia, coarctation of the aorta and vegetations on the mitral and aortic valves. Foken[10] also records 2 cases of the "adult" type of coarctation, 1 with hemolytic streptococcus vegetations at the site of the stenosis and the other with subacute bacterial endocarditis involving the mitral and aortic valves and the aorta where the stenosis occurred, the infecting organism in the latter case was not determined; blood cultures were sterile.

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ON THE MEANING OF EXTRASYSTOLES.

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ALTHOUGH much effort has been expended on the problem of extrasystoles, their significance remains ill-understood. It is known

that the several experimental conditions in which these phenomena are observed cannot be brought into parallelism with clinical conditions.[1] Neither high pressures;[2] nor excessive hypercalcemias nor far-pushed intoxications of various kinds can adequately account for the production of premature contractions. Highly abnormal conditions cannot be called upon to explain such very common events as are extrasystoles. Furthermore, partly in consequence of this situation, we do not possess any discriminative principle by which to group them in regard to their clinical significance, prognostic or otherwise.

Topical diagnosis has gone far toward localization of the focus from which premature contractions issue. It is possible not only to localize such a focus in the right or left auricle, right or left ventricle, *A–V* node or upper junctional tissues, but to establish its place, although only roughly, within one chamber. Nevertheless, without knowledge of the pathogenesis, this refined anatomical diagnosis has been of but small clinical value, and distinctions based only upon anatomic diagnosis have not been successful.

Thus the view that auricular extrasystoles have a more serious significance than ventricular ones, has not been substantiated. It is clear that the value of an anatomic diagnosis of extrasystoles would lie in the fact that they reveal pathologic changes in the focus of their origin. But evidence for such connection we do not possess. There remain the other possibilities that they are signs of an increased myocardial excitability (a stand taken by Wenckebach[3]) or that they are expressions of increased action of certain extracardial nerves (positive bathmotropic influence).[4] Evidence indeed has been brought forth for the latter possibility, and this evidence is confirmed by everyday clinical observation (well-known reflex-extrasystoles connected with peripheral irritating foci, and so forth). However, it is obvious that extrasystoles are sometimes associated with serious organic disease and that at other times they are transitory and such association cannot be traced. Whereas at one time they are precursors of multiplication and ventricular fibrillation,[5] at another they vanish without such outcome.

We must recognize therefore that there is a difference between the various forms of extrasystoles from the clinical point of view and that they cannot be equivalent. Some discriminating principle must be looked for, and it seems to me that scattered experimental facts (such as the behavior of the chloroformed heart)[6] and some clinical observations point toward a distinction between *unifocal and multifocal ventricular extrasystoles* as being such a discriminating principle. My assumption is that unifocal extrasystoles, those arising in a single ventricular focus, are due mainly to disturbances of innervation; while multifocal extrasystoles, those originating in two or more ventricular foci, develop on the basis of some organic change which modifies myocardial irritability. Thus, the two groups

may be separated according to their prognostic and therapeutic implications.

With this presupposition in mind I have surveyed 100 cases, encountered at random in an ordinary hospital service. Certain facts will become apparent, in considering these cases of extrasystoles from four stand-points: (1) By dividing them into the two groups of uni- and multifocal extrasystoles and determining the conditions with which they are associated; (2) conversely, by arranging them according to clinical conditions and asking how many of the group show the one or the other type of premature contractions; (3) by arranging them according to outcome; and (4) according to other electrocardiographic abnormalities.

In this series the number of cases with unifocal extrasystoles is two-thirds of the total number; sixty-six, against thirty-four of the multifocal type.

TABLE I.—DIVISION ACCORDING TO NUMBER OF FOCI.

		Unifocal extrasystoles.		Multifocal extrasystoles.	
Diagnosis.	Total.	No.	Per cent.	No.	Per cent.
Arteriosclerosis	44	26	59	18	41
Pancarditis of rheumatic origin	17	6	35	11	65
Pancarditis of nonrheumatic origin	9	5	56	4	44
Thyrotoxicosis	6	5	83	1	17
Subacute bacterial endocarditis	3	3	100		
Lues (mesaortitis, etc.)	6	6	100		
Obesity	3	3	100		
Miscellaneous (anemias, cholelithiasis, etc.)	12	12			
	100	66		34	

Table I simply shows that in this particular series there is a larger percentage of diseases involving organic myocardial changes represented in the group of multifocal extrasystoles than in the group of unifocal ones, and it also shows that diseases *not* involving such organic changes, such as those classified as "miscellaneous," do not appear among the group of multifocal premature beats.

It is also to be seen that the majority of extrasystoles observed in rheumatic pancarditis are multifocal. It is further apparent that in the two other groups representing myocardial affections a large percentage of extrasystoles are multifocal whereas in the groups not corresponding to myocardial disease such multifocal premature beats are absent or at least very rare.

Next we may briefly consider the outcome to determine the prognostic value of this discrimination.

TABLE II.—OUTCOME IN THE TWO EXTRASYSTOLE GROUPS.

	(During hospital observation.)	
Total number of cases with unifocal extrasystoles.	Fatal outcome.	Nonfatal outcome.
66	16 (24%)	50 (76%)
Total number of cases with multifocal extrasystoles.		
34	15 (44%)	19 (56%)

When the cases are divided into individual diagnostic groups the higher mortality among cases showing multifocal ventricular extrasystoles becomes more apparent.

TABLE III.

Diagnostic group.	Unifocal extrasystoles.		Multifocal extrasystoles.	
	Fatal.	Nonfatal.	Fatal.	Nonfatal.
Arteriosclerosis	6	20	7	11
Pancarditis of rheumatic origin	1	5	7	4
Pancarditis of nonrheumatic origin	..	5	..	4
Thyrotoxicosis	..	5	1	
Subacute bacterial endocarditis	3			
Lues	3	3		
Obesity	..	3		
Miscellaneous	3	9		

The 3 cases classed as "miscellaneous" which ended fatally were: generalized carcinomatosis, pernicious anemia, and nephrosclerosis with renal insufficiency and uremia. The heart was not involved.

The autopsy records of the last mentioned 3 cases, as already stated, show no cardiac involvement. In the 3 fatal cases of luetic aortitis, syphilitic mesaortitis and thickening and retraction of the aortic valves were recorded, with left ventricular hypertrophy, but with no histologic changes in the myocardium. The autopsies of all other fatal cases revealed myocardial changes, although it is to be noted that well-circumscribed pathologic areas in that tissue, such as myomalacial foci, were seen only in those hearts which exhibited multifocal extrasystoles.

Some additional information might be expected by listing electrocardiographic observations; for very often the electrocardiogram reveals events in the tissue not traceable by the histologist. It is interesting to find that there is not a single case of multifocal extrasystoles in this series which was not associated with other marked deviations from the physiologic electrocardiogram. Abnormalities of conductivity—complete A–V dissociations, bundle-branch blocks, severely depressed intraventricular conductivity and arborization blocks—and abnormalities of irritability—auricular, nodal and fascicular extrasystoles; auricular fibrillations; heavy preponderances of the right or left ventricle (with electrical axes of $-20°$ and even more) are encountered. T-wave diphasicity and T-wave negativity in more than one lead are constant concomitant phenomena. On the other hand, while many of the unifocal extrasystoles also are accompanied by auricular fibrillation, arborization block, deviations of the electrical axis in a marked degree and some minor changes, a large number are free from such associations. In considering this, it must be kept in mind that in the course of a hospital service extrasystoles are liable to be discovered by the electrocardiograph, as additional incidents, so to speak, whereas in

many of the cases seen only ambulatorily these escape notice. Thus, the percentage of cases with extrasystoles showing absolutely no cardiac involvement must be very much higher than would be suggested by this series. Making this allowance, the discovery that *every case* of multifocal extrasystoles listed in this series has shown some myocardial lesion, detected either by the electrocardiograph or by autopsy, is not without its significance.

Summary. 1. Diseases representing pathologic changes in the myocardium show a greater percentage of ventricular extrasystoles arising in multiple foci than extrasystoles arising in one focus.

2. Diseases not involving the heart are *not* accompanied by multifocal ventricular extrasystoles.

3. Unifocal extrasystoles sometimes, multifocal extrasystoles always, are accompanied by myocardial disease.

4. The prognostic significance of multifocal ventricular extrasystoles is much graver than that of the unifocal premature beats.

5. It is suggested that multifocal extrasystoles are expressions of some change in the myocardium (possibly some change in its nutrition) resulting in an increased irritability of that tissue.

6. Unifocal extrasystoles, on the other hand, may very well be but expressions of extracardial stimulation.

Experimental work is needed to prove or disprove the validity of this discriminating principle based on the inequality of unifocal and multifocal ventricular extrasystoles. I suggest that meanwhile the clinical value of this discrimination be tested.

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DIAGNOSIS AND TREATMENT OF SEASONAL HAYFEVER.*

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In 1911, Freeman and Noon[1] of England published two papers describing the successful treatment of hayfever by the injection of extracts of pollen, on the hypothesis that they were dealing with an anaphylactic phenomenon. Since then numerous articles, by many different investigators, have appeared, dealing with this subject. In the present paper we do not intend to cover this literature extensively, but will confine ourselves chiefly to our own personal experience in this work during the past sixteen years, and present in detail a careful study of 980 cases observed and treated during the season of 1926.

A short paper in 1915, by R. A. Cooke,[2] gave the results of treatment of a series of hayfever cases in 1911, 1912, 1913 and 1914, and a longer article in 1916,[3] set forth the basic principles which we have since followed.

Hayfever manifests itself clinically in three forms, designated spring, early and late hayfever. The spring season lasts from early April until early June, the early season from mid-May to the end of July, and the late season from the middle of August to frost. A patient may present any one or all of these forms and in any combination. An idea of the relative frequency of each may be gained from Table I showing the number of cases of each observed during the past three years.

TABLE I.—FREQUENCY OF SPRING, EARLY AND LATE HAYFEVER.

Variety.	Number of cases.		
	1924.	1925.	1926.
Spring	11	10	9
Spring and early	15	15	39
Spring, early and late	45	41	51
Spring and late	6	4	3
Early	198	206	192
Early and late	122	119	172
Late	508	561	514
Total	905	956	980

More than half the cases are of the pure late variety and, as there is no late season in Europe, hay fever is much less prevalent there than in America.

* Read before the New York Academy of Medicine, Section of Medicine, March 15, 1927.

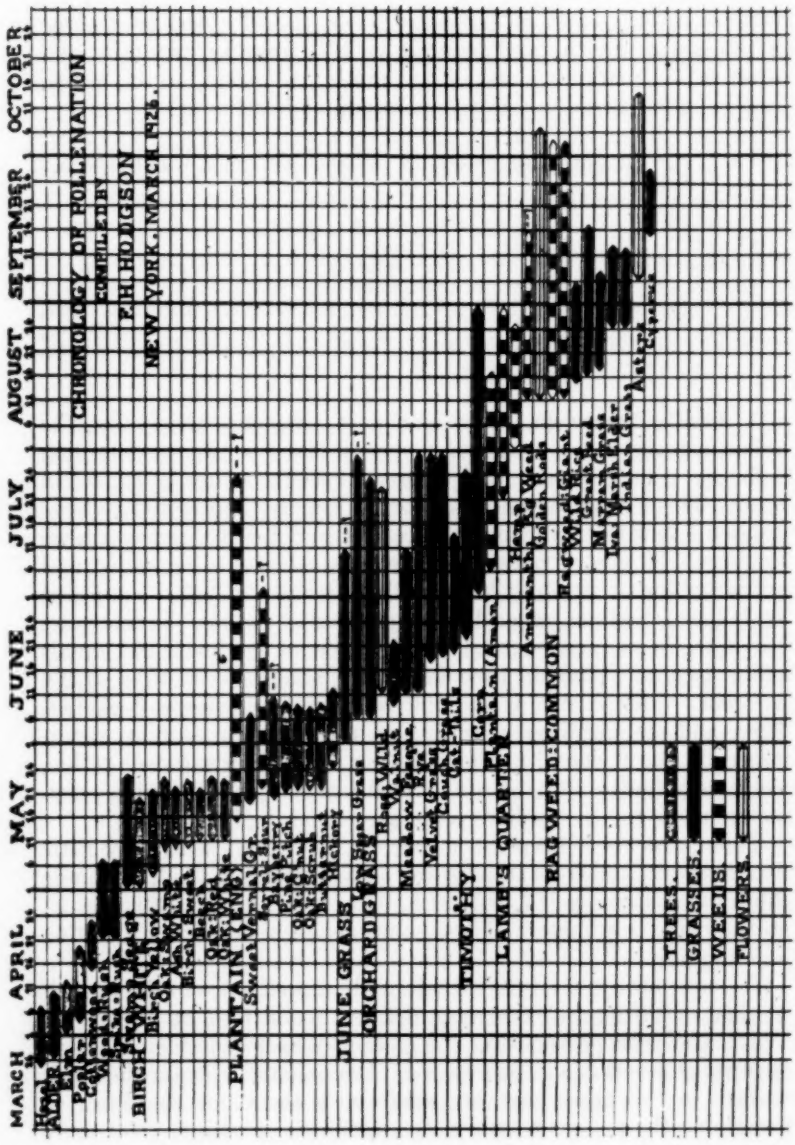
1. **Specific Causes of Hayfever.** In our original article are listed 26 pollens which had given reactions in early and late cases. Since then, we have studied several hundred other pollens, discarding those which seemed unimportant, and retaining for use any which might prove of clinical value. Since 1924, Prof. F. H. Hodgson, of the Montclair Academy, has worked with us as field botanist from early in March until October. He sends us a daily report giving the trees, grasses, and weeds pollenizing at the time, and the relative quantity and importance of each. These daily notes have been consolidated, and from them Professor Hodgson has made a chart showing the approximate pollenating season of all the important flora in this vicinity.

The United States may be roughly divided into seven major areas, differing widely from each other in their flora. The area with which we are mainly concerned stretches from Canada to the Ohio River and westward to the Mississippi River Valley. Throughout this entire district the flora and dates of pollenation are much the same, although variations of a week or ten days may occur, depending on the temperature and rain-fall. The chief variation will be found among the trees. The order of succession remains the same.

The other major areas are: (2) South of the Ohio River and east of the Mississippi River; (3) from the Mississippi River Valley to the Rocky Mountains; (4) Southern Texas; (5) Arizona and New Mexico; (6) Southern California; (7) Northern California, Oregon and Washington. Piness[4] gives a list of the important pollens of southern California, and refers to the literature of pollen surveys in other parts of the country.

The survey is confined to those pollens which are air-borne, and which occur in sufficient quantities to make them probable etiological factors. In conjunction with the pollen chart may be used an individual chart, kept by the patient, showing the onset and offset of his trouble, with daily record of its severity. This can be checked against the pollen chart, and the probable sources of trouble narrowed to a small field.

In our previous paper it is stated that the various grass pollens, while botanically different, are biologically the same, and that treatment with one will protect against all, the same being true with the several varieties of ragweed and the many varieties of goldenrod. Subsequent clinical experimentation by ourselves and by Brown[5] in 1926 have proved this to be the case, and it also holds true for the different varieties of tree pollens, such as the birches, oaks, and hickories, which we began to use in 1921. This rule only holds true for closely related species of the same genus. We cannot immunize against hypersensitiveness to birch pollen with an extract of oak pollen, nor against plantain or ragweed hypersensitiveness with grass pollen. Since 1923 we have used timothy pollen alone for our grass cases.


CHRONOLOGY OF POLLENATION
COMPILED BY
P.H. HODGSON
NEW YORK. MARCH 1925.
MARCH
APRIL
MAY
JUNE
JULY
AUGUST
SEPTEMBER
OCTOBER
BIRCH
PLANTAIN
JUNE GRASS
ORCHARD GRASS
TIMOTHY
LAMB'S QUARTER
RAGWEED & COMMON
TREES.
GRASSES.
WEEDS.
FLOWERS.

The relative importance of the various pollens is shown in the following table, giving the number of cases in which they were used. They occurred in almost every possible combination; for instance, in 427 cases of early hay fever, timothy was used alone in 186 cases; timothy and plantain in 175; timothy, plantain, and sorrel in 31; plantain alone in 5; timothy, plantain, sorrel, sedge, hickory, and others in various combinations in 30 more.

TABLE II.—NUMBER OF CASES IN WHICH POLLENS WERE USED.

Pollen used in	Cases.	Pollen used in	Cases.
Ragweed	696	Sorrel	50
Timothy	420	Ash	41
Plantain	237	Sedge	23
Hickory	62	Goldenrod	14
Birch	59	Poplar, Elm, Maple, Cottonwood, Sage, Indian Grass, Maram Grass, Dahlia, Sunflower, etc., used in occasional cases.	
Beech	58		
Oak	56		

2. **Specific Treatment.** *Preparation of Extracts.* Originally, the pollen was extracted with 0.8 per cent NaCl solution containing 0.25 per cent trikresol, and filtered through a sterile Berkefeld filter. This extract deteriorated rather rapidly, and in 1921, Coca[6] devised a new method which overcame this difficulty, and which we now use. 30 gm. of pure pollen are washed with ether, dried and extracted for twenty-four hours with a liter of a solution composed as follows: Sodium chloride 0.5 per cent; sodium bicarbonate, $NaHCO_3$, in such concentration that 10 cc. of the final fluid equals about 3 cc. of $\frac{N}{10}$ alkali; carbolic acid in final concentration of 0.4 per cent. This extract is then filtered through a sterile Berkefeld filter, and standardized according to the nitrogen content, determined by the Kjeldahl method. Using timothy or ragweed pollen, we usually find a content of 0.3 to 0.4 mg. N. to the cubic centimeter, while the tree pollens often give much higher figures.

This extract will keep for a year in the icebox with very little deterioration, and from it, with the same extracting fluid, are made dilutions containing 0.2, 0.1, 0.05, 0.01, 0.001, and 0.0001 mg. N. to the cubic centimeter. These solutions are used for both testing and treating.

We have always used the intradermal, in preference to the scratch method of testing, as it is more delicate (confirmed by Brown[7] in 1922), and with proper care, the greater danger of inducing a constitutional reaction can be avoided. Preliminary tests on the outer surface of the upper arm are made with the 0.001 solutions, to determine the pollens to which the patient is sensitive. Not more than six of these should be done at once, and at least ten minutes are allowed to elapse before the introduction of further tests. Three series of six tests each are the maximum to be done at one sitting. Positive reactions are denoted as slight, moderate, marked, and

marked plus. Slight reactions may be disregarded, except as an indication to test with a stronger solution. Moderate reactions are round in outline, with a surrounding area of hyperemia and itching. Marked reactions are distinguished by distinct pseudopods, in addition to the hyperemia and itching, and marked plus reactions show a diameter of an inch or more.

A marked skin reaction almost invariably means that the patient will show clinical evidence of hayfever if exposed to that pollen in sufficient concentration. Exceptions to this rule are as follows:

(*a*) Those patients who have not yet developed a mucous membrane sensitivity (potential hayfever patients).

(*b*) Those who have had hayfever, but have lost their mucous membrane sensitivity, still retaining that of the skin.

(*c*) A small group who may give both skin and eye reactions to the pollen extract (sometimes in very weak solution), and yet show no clinical evidence of hayfever. The mechanism of their protection is at present entirely unknown.

When we have determined the pollens we intend to use, further tests are made with 0.0001 and 0.01 solutions, to measure the degree of sensitiveness. The 0.01 solutions should be used with care, and only one test done at a time, as they may precipitate a constitutional reaction. Ophthalmic tests may also be done to further confirm the degree of sensitiveness. A little of the 0.001 solution is dropped in the eye, and, if positive, will cause reddening and itching of the caruncle and conjunctiva, with irritation of the nose on that side, and sneezing. The reaction should be terminated by a drop of epinephrin. It requires a stronger solution to elicit a reaction in the eye than in the skin.

Patients are classified according to the scheme shown in Table III.

TABLE III.—CLASSIFICATION OF PATIENTS ACCORDING TO SENSITIVENESS.

AA.	A.	B.	BC.	C.	D.
0.00001 marked	0.0001 marked	0.001 marked	0.001 marked	0.001 mod.	0.01 mod.
0.0001 marked plus	0.001 marked plus	0.01 marked plus	0.01 marked	0.01 marked	0.05 mod. or marked

Classes AA and A are considered extremely sensitive; class B, sensitive; classes BC and C, average; and class D, relatively insensitive. In 1926, 1070 cases (counting each season of each patient as a separate case) were divided as shown in Table IV.

As a rule, patients vary little from year to year in their degree of sensitiveness, unless they begin to develop a permanent immunity when they gradually fall into a less sensitive class; nor do they show any marked diminution of sensitiveness while under treatment, even though free from clinical symptoms.

TABLE IV.—ANALYSES OF 1070 CASES IN 1926.

Class.		AA.	A.	B.	BC.	C.	D.
Season—Spring		0	1	1	19	55	14
Early		1	15	55	117	149	56
Late		1	12	105	216	163	90
	Total	2	28	161	352	367	160

Very sensitive	AA + A	30	= 3 per cent
Sensitive	B	161	= 15 "
Average	BC + C	719	= 67 "
Less sensitive	D	160	= 15 "
	Total	1070	= 100 per cent

The determination of the degree of sensitivity and the division into classes is undertaken to guide us in our dosage. At the present time this is far from satisfactory, and we can only say in general (as we did in 1916) that the more sensitive the case, the smaller will be the dose required to keep the patient free from symptoms, and the more apt will that patient be to develop a constitutional reaction. Charts I and II, giving dosage and constitutional reactions in 1922 and in 1926, bring out these facts very clearly.

CONSTITUTIONAL REACTIONS.

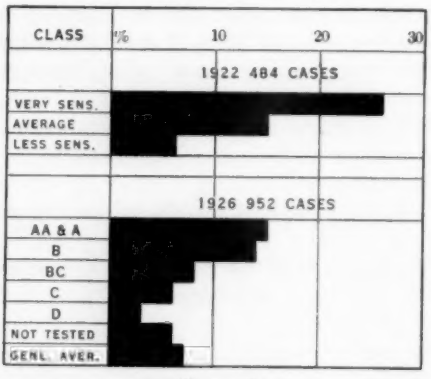


CHART I

The chief difficulty encountered is with the cases in classes AA, A, and B, nearly half of which will require doses much larger than we would expect in order to obtain a good result, and will tolerate these larger doses without developing constitutional reactions. At present, we are unable to separate, by tests alone, these cases from the true sensitive patients who cannot tolerate large doses and who do not require them. Here the clinical experience of a previous year's treatment is of great value, as we can modify our judgment of the proper dosage with the knowledge thus gained.

In the average and less sensitive cases, we meet with fewer exceptions to the rule, and can usually proceed with our regular schedule.

Prophylactic treatment is the method of choice, and should be begun about ten weeks before the season opens, injections being given at four- to seven-day intervals. The maximum dose should be reached just before the season, and should be repeated at five- to seven-day intervals, until the pollen disappears from the air. As a rule about 20 injections are required. Phylactic treatment is less satisfactory, but is used for those patient who present themselves during the season. It is interesting to note that, with the increased knowledge of hayfever among the laity, comparatively few patients now wait until their symptoms have developed before coming in for treatment. The first dose is repeated on three successive days, then larger doses are given at gradually lengthened intervals. Results are less satisfactory, but the discomfort is often materially reduced.

DOSAGE.

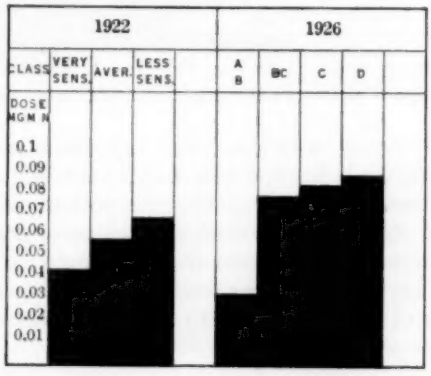


CHART II

We have had no experience with Duke's[8] method of treatment, beginning the end of July and giving one or two doses a day; but feel it is theoretically unsound, because of our poorer results in phylactic dosage, and because of the increased liability to constitutional reactions when injections are given so close together.

Table V presents a fair working scheme of dosage in the various classes, but it must always be borne in mind that frequent modifications may be necessary. Following a marked local or a constitutional reaction, the next dose should be reduced, and subsequent increases made more gradually.

Patients sensitive to several pollens should receive a mixture of the extracts of those pollens. The most difficult to handle are the spring, early and late cases, where the tree pollen extract must reach its maximum early in May, the grass pollen or plantain late in May, and the ragweed by the middle of August. With care and experience, it is possible to work out such mixtures and schedules,

so that many of these patients can be kept free from symptoms all summer long.

TABLE V.—PROPHYLACTIC TREATMENT, AVERAGE DOSAGE FOR VARIOUS CLASSES.

	AA.	A.	B.	BC.	C.	D.
			Injections.			
Day of test . .	0.	0.	0.	0.0001	0.0003	0.001
1st injection .	0.00005	0.0001	0.0001	0.0002	0.001	0.003
2d " . .	0.0001	0.0002	0.0002	0.0004	0.003	0.006
3d " . .	0.0002	0.0003	0.0004	0.0007	0.006	0.01
4th " . .	0.0003	0.0005	0.0007	0.001	0.01	0.015
5th " . .	0.0005	0.0007	0.001	0.002	0.015	0.02
6th " . .	0.0007	0.001	0.002	0.004	0.02	0.03
7th " . .	0.001 *	0.0015	0.004	0.007	0.03	0.04
8th " . .	....	0.002	0.007	0.01	0.04	0.06
9th " . .	....	0.003	0.01	0.015	0.05	0.08
10th " . .	....	0.004	0.0125	0.02	0.06	0.1
11th " . .	....	0.006	0.015	0.03	0.08	0.12
12th " . .	....	0.008	0.02	0.04	0.1*	0.16
13th " . .	....	0.01 *	0.025*	0.05*		0.2 *

* This dose continued at four to seven-day intervals during the season.

3. **Reactions.** Local reactions from injections ordinarily cause little discomfort, and disappear within twenty-four hours. If a marked local reaction occurs, the succeeding dose should be decreased, and subsequent increases made more gradually. Constitutional reactions are more serious, and should be avoided as far as possible. They usually occur from one of three causes:

(*a*) Injection of a larger dose than the patient can tolerate, or too large an increase over the previous dose.

(*b*) The accidental introduction of the extract directly into a vein.

(*c*) The change to a fresher and more powerful extract.

Constitutional symptoms may occur after any injection. Chart III shows the probable causes in 96 reactions in 1926, and also the number of the injection they followed.

As shown in Chart I, they occur more frequently in the very sensitive cases.

The reaction manifests itself within half an hour of the injection, and, the longer it is delayed, the less severe it is apt to be. The first symptoms are itching of the palms of the hands, sneezing, and an irritative cough. This may subside in a few minutes, or may go on to an attack of severe asthma, general urticaria, and swelling of the tissues of the neck and face. At the first sign of such a reaction, 0.5 cc. of epinephrin should be given subcutaneously above the site of the pollen injection; and, if the reaction does not begin to clear up in a few minutes, a tourniquet should be placed about the arm above the injection, and 1 cc. of epinephrin given in the other arm. In extreme cases, epinephrin has been administered intravenously. It should be made an invariable rule never to make

any pollen test or administer any pollen extract unless there is a bottle of epinephrin at hand.

CONSTITUTIONAL REACTIONS 1926.

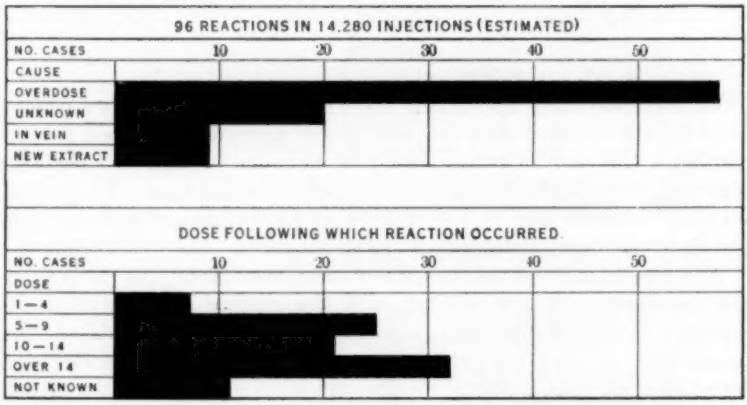


CHART III

Constitutional reactions occur in about 10 per cent of all patients treated and follow less than 1 per cent of all injections. Certain patients are more prone to develop them than others, and those showing such a tendency should be treated with special care. Clinical experience is of great value in avoiding reactions, as is shown in Chart IV, where a steady decrease in percentage is evident.

CONSTITUTIONAL REACTIONS.

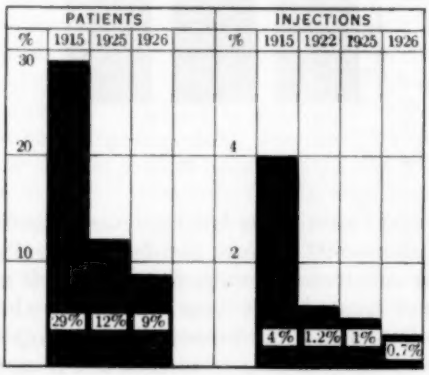


CHART IV

In none of our cases, some of which have been treated for fifteen years, have we seen any evidence of any functional or organic disturbance that could conceivably be traced to the inoculations, other than the specific reactions above mentioned.

4. **Results of Active Immunization.** In their original article, Freeman and Noon proposed a classification of results divided into four groups:

+++, hayfever absent or so slight as to be negligible.
++, hayfever greatly relieved.
+, hayfever slightly relieved.
−, hayfever unrelieved.

We have adopted this classification in all our studies, as we believe it to be the clearest and simplest so far proposed. Stated in percentages, the +++ group would be between 90 and 100 per cent relieved; ++, 75 to 90 per cent; + below 75 per cent. In general, we may consider the +++ and ++ results as satisfactory, and the + and − unsatisfactory.

The results depend on the type of case, the severity of the season, the intelligence of the patient, and the clinical experience of the doctor. It is easier to secure a good result in the spring cases than in the late, as they are exposed to a smaller amount of pollen and for a shorter time. They require much smaller doses of extract. Chart V shows the satisfactory results in each season for 1924, 1925 and 1926.

SATISFACTORY RESULTS OF TREATMENT.

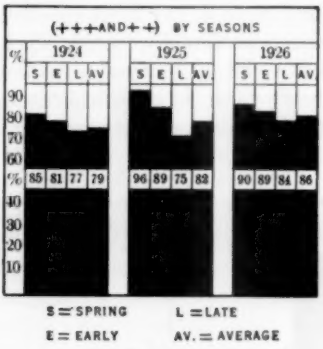


CHART V

One hundred and twenty-nine late hayfever patients, treated personally in 1926, showed 90 per cent satisfactory results as compared with 84 per cent satisfactory results for the general average of late hayfever patients treated that year, many of whom had their extract sent to them and administered their own injections.

Chart VI shows the results of treatment in Freeman and Noon's original series, our own earliest series, and in 1915, 1922, 1924, 1925 and 1926. We have included in these figures only those cases which have had at least three weeks of preseasonal treatment. As should be expected, the percentage of satisfactory results shows a gradual improvement, and in general we may say that 85 per cent of the cases are successful with 15 per cent unsuccessful. In the latter

cases, we have not discovered all the causative factors or else our dosage has been in error.

RESULTS OF TREATMENT.

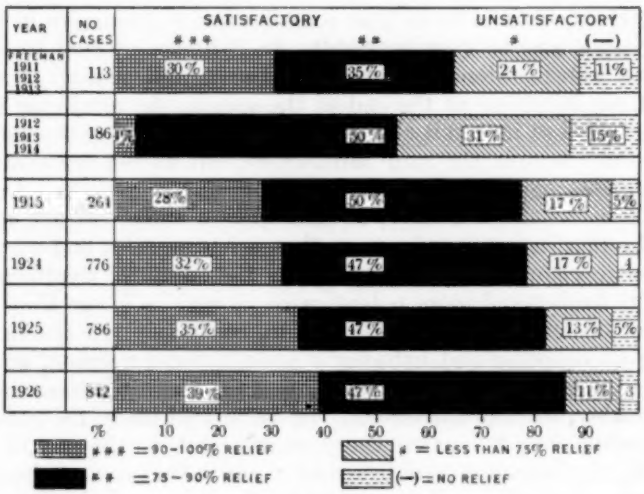


CHART VI

Asthma. About 30 per cent of all hayfever patients also suffer from pollen asthma. In 1925, 125 patients out of 397 gave such a history. Seventy-five per cent of these were relieved by the injections, while 25 per cent continued to have asthma in greater or less degree. In 1920, R. A. Cooke[9] reported a series of 135 pollen asthmas, in which 53 per cent were entirely relieved by treatment.

5. **Duration of Immunity.** It is undoubtedly true, as stated by Freeman, that many patients successfully immunized one year will carry over partial or complete immunity for the next one or two years. A few remain permanently free, but the majority gradually return to their former condition. It is also true that many spontaneous cures occur. Unfortunately, the skin hypersensitiveness is apt to remain after the mucous membrane hypersensitiveness has disappeared, and it is impossible to assure such a patient with positive reactions that he will escape hayfever. When the ophthalmic and skin reactions become negative, it is perfectly safe to give such assurance. It is our belief that children, who have had the disease but a short time, stand a better chance of permanent cure after two or three years' treatment than do adults, who have suffered for many years, but we have no accurate figures to substantiate such a belief.

6. **Treatment by Monthly Injections.** While our present method of treatment is very satisfactory, as far as the relief of symptoms is concerned, we cannot feel that we have reached our goal until we

can promise our patients a reasonable hope of permanent cure. Many years ago, we noticed that some of our horse-sensitive cases, who were kept permanently immunized by large injections once a month, showed a tendency to become cured after several years. It therefore occurred to us that a similar line of treatment in hay-fever might lead to a similar result. In 1920, we selected 10 or 12 patients who had done well under treatment, and, instead of stopping their injections at the end of the season, the maximum dose was repeated at intervals of three or four weeks during the winter. The results were in the main satisfactory, but we did not continue the experiment on a large scale because of two drawbacks. In the first place, we did not have, at that time, a stable extract which would retain its potency for more than a few months, and we were obliged to change several times during the course of treatment to extracts fresher and more potent, with no way to gauge the exact amount of deterioration. We therefore constantly ran the risk of giving an overdose and inducing a constitutional reaction, and as we used a maximum dose at each injection, these reactions could, conceivably, be very unpleasant. In the second place, the patients occasionally forgot to come every month, and, at the end of two months, the immunity had decreased so much that it was necessary to start again with small doses weekly, thus losing all the time and benefit which had been gained.

With the introduction of Coca's solution for the extraction of the pollen, we obtained a stable extract, which removed the chief objection to the monthly treatments. Two years ago, we again started our experiment with 70 cases, 50 of whom persevered, and the results have been distinctly encouraging. All of these patients were treated in our office and carefully observed.

The method of treatment is very simple. Instead of discontinuing at the end of the season, the patient is directed to return once a month throughout the year, and each time receives the maximum dose attained during the season. As the extract deteriorates a little, even under the best of care, this dose may be increased slightly with each injection. When fresh extract is made up, it should be added gradually; for instance, 0.1 cc. new extract and 0.9 cc. of the old extract; then 0.3 and 0.7; 0.6 and 0.4; and, finally, a full dose of the new extract. In this way, we minimize the danger of constitutional reactions.

During the season it may be necessary to give injections oftener than once a month, and the interval between them is determined by clinical symptoms. The average total dose is larger under the monthly system, being 0.13 mg. N. at the beginning and in mid-season as compared with 0.07 and 0.09 mg. N. in the same cases during the previous season under weekly injections.

While the ultimate aim of this method is a permanent cure, it is essential that the clinical relief during the season should be at least

as satisfactory as with seasonal injections. Of the 50 cases in the group under consideration, 86 per cent reported satisfactory results in 1925 with weekly injections; while 95 per cent of the same 50 cases were satisfactory in 1926 after a year of monthly injections. This shows a definite improvement with the latter form of treatment. Constitutional reactions were slightly more frequent, occurring in 0.66 per cent of the injections, as compared with 0.13 per cent the year before in the same cases. With care and further knowledge, this figure should be reduced.

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A NOTE ON THE SUBJECTIVE AUDITION OF PATHOLOGIC PULMONARY SOUNDS.

By Nicholas Michelson, M.D.,

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The physician is frequently asked by a tuberculous individual why, when in a recumbent posture, with the head on a pillow, he hears resounding seething noises which disappear when he is in the erect posture. Apparently the obstruction of the external auditory meatus causes a temporary and nonpathologic intensification of the bone-conducting sound apparatus. It is a known fact that normally the tone of a vibrating tuning fork, when applied to the frontal region, will be heard loudest with the closed ear. Sounds emanating from the mouth appear intensified in an ear shut with the finger, an observation that any alert child usually makes while singing or whistling and rhythmically clasping the hands upon its ears. The introspective intelligent tuberculous patient is able to differentiate the transmitted fine bubbling râles from the sounds created by pulsations of bloodvessels which frequently annoy sleepless individuals. Such patients can also distinguish the râles from the sensation of to-and-fro movements of fluid in the ear, due to a transudation of serum into the tympanum, caused by catarrh of the Eustachian tubes with subsequent closure, and from the various

subjective acoustic manifestations of inflammatory middle-ear disease. He is aware of the leather-like pleural creaks. He compares the adventitious bronchial sounds with the cooing of doves. Persons with hydropneumothorax not only feel the impact of fluid during vigorous movements, but actually hear the splash.

As all of these subjective acoustic phenomena not only harass the patient but are also of some diagnostic value, their study is justified. In this paper we shall confine ourselves to pathologic sounds transmitted from the lungs, and shall consider the loudness of pathologic pulmonary sounds, the mechanism of their conveyance and their practical significance.

More or less intense sounds arising in the diseased respiratory organs may be detected by the examiner quite a distance from their origin. Moist râles, pleuritic squeaks, rhonchi, etc., are very often audible by oral auscultation, with or without the use of stethoscope. Pathologic intrathoracic sounds may be conducted through the bony framework of the chest along the humerus, and may be auscultated over the olecranon process, either from the homolateral or contralateral hemithorax. Such loud noises are frequently heard by the phthisical patient. In other instances in which faint râles are not heard by the patient ordinarily, these may become audible when the patient compresses his tragus.

In order to verify this subjective acoustic phenomenon the following experiment was performed: A series of vibrating tuning forks were alternately placed on the author's vertebra prominens, and after the tone had become imperceptible the external auditory meatus was occluded. Thereupon, the tone again became audible; for example, after the tone of tuning fork C–2 (512 vibrations) had become extinct, closure of the external auditory meatus again rendered it audible for a period of twenty seconds.

We may assume that all the sounds discussed here follow the law of forced vibrations, and that the air column contained in the closed auditory canal acts as a resonator.

The objective evidence of intense pathologic pulmonary sounds is not in all cases in direct proportion to the subjective acoustic sensations of the tuberculous individual. Evidently the hypersensitiveness of the patient and the difference between the normal and the pathologically modified sound apparatus are responsible for the very variable acoustic effects. In a previous paper[1] it was pointed out that tuberculous patients with otitis media can often hear, with the diseased ear râles produced in their lungs. This is due to the prolonged and intensified bone conduction which favors the audition of vibrations transmitted to the skull.

Conclusions.—Analyzing the various possibilities, both theoretically and clinically, we may conclude that exaggerated subjective response to pathologic sounds conveyed from diseased lungs may take place:

1. In a normal ear by the obstruction of the external auditory canal.

2. In the presence of a retracted drum, due to chronic catarrh of the Eustachian tube.

3. In inflammatory affections of the middle ear.

Thus, subjective audition of pathologic pulmonary sounds may give rise to more than one interpretation, thereby limiting its diagnostic worth. Moreover, the amplification of râles in one ear does not determine the location of the pulmonary involvement. This can be readily demonstrated in a patient with a strictly unilateral lung lesion. For instance, when the right lung is diseased, and the left tragus is compressed, râles may become audible in the left ear. On closure of the homolateral ear the râles would be heard there also.

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In the present edition the author has added a section dealing with the glands of internal secretion and there are other evidences of revision. Important statements are italicized so that the student may review any subject in a short time. The reviewer is unable to find mention of roentgenography of the tubes but otherwise the book is all that can be expected of a work of this kind. F. B.

Surgical Applied Anatomy. By Sir Frederick Treves, Bart. Eighth edition, revised by C. C. Choyce, C.M.G., C.B.E., B.Sc., N.Z., M.D. Edin., F.R.C.S., Eng. Pp. 727; 162 illustrations. Philadelphia: Lea & Febiger, 1927.

This is the eighth edition of a work that was a classic more than forty years ago. It still deserves its place in the first rank of text books on this subject. It gives a collection of facts and presents the same in a way that is not found in any other book, at least known to the reviewer. This correlation of anatomical facts and surgical conditions is unique with this writer. Ordinarily the student of human anatomy has a rather vague notion that at some time in the future he will need his anatomical knowledge. What he learns, however, as a student, proves of little use until he has learned to apply it. This work marshals the essential and important features that have to do with each and every condition under discussion. It is an admirable adjunct to the armamentarium both of the student, the hospital resident and the busy surgeon. More, it is a great help and incentive to a teacher of surgical subjects. Can a reader but picture the reasons why things occur he can the more easily remember the facts in the case. This book makes applied anatomy interesting. E. E.

MEDICAL SCIENCE FOR EVERYDAY USE. By SHIELDS WARREN, A.B., M.D., Pathologist, Palmer Memorial Hospital, Boston. Pp. 178. Philadelphia: Lea & Febiger, 1927. Price, $2.00.

THIS booklet is a revision of lay articles on subjects of current medical interest that have appeared in the Boston *Sunday Herald*. The first eight of its twenty-three chapters are devoted to such topics as the growth and health of children, work and exercise, diet, sleep and so forth; the remainder to the commoner diseases. Granted the desirability of offering this kind of information to the public through such channels, a little knowledge being proverbially dangerous, medical men must approve of the accuracy and clearness of the text. A thorough comprehension by the average lay reader, on the other hand, would indicate an educational standard perhaps only reached in the Hub of the Universe. E. K.

MANUAL OF OPERATIVE SURGERY. By SIR HOLBURT J. WARING, M.S., M.B., B.Sc., F.R.C.S. Sixth edition. Pp. 868; 618 illustrations. New York: Oxford University Press, American Branch, 1927.

THIS, the sixth edition, has been very thoroughly revised. A number of operations not included previously have been added and many operations that have been found, through the test of time, to be obsolete have very properly, been discarded. Some 618 illustrations lend much to the value of the work. The style of the writer is pleasing as far as can be in the presentation of cold, hard unyielding facts. The arrangement of the material is good and the description of operations is clear, concise and amply sufficient for use in the operating room. Chapter II deals with general surgical technique, such as sterilization, the making of sponges, swabs, etc., the clothing of the surgeon, ligature and suture material, operating room furniture, etc. The book itself is of a handy reference size and the paper and printing are first class. E. E.

ELEMENTS OF SURGICAL DIAGNOSIS. By SIR ALFRED PEARCE GOULD, M.S., F.R.C.S. Sixth edition. Pp. 739; 20 illustrations. New York: Paul B. Hoeber, Inc., 1927. Price, $5.00.

FORTY years ago this book first appeared on the market. The fact that after forty years surgical diagnosis is still to be attained only by methodical and painstaking complete examinations has led to the text and arrangement of the work to be maintained to a great extent in its original form. That there is no royal road to successful

diagnosis even in this day of our perfected laboratory diagnosis, makes this book still an extremely valuable one. There has been added, in this, the sixth edition, new subjects such as Labyrinthitis, Cæcal Stasis, Perthes' Disease, and much new material has been added to the revised matter on Surgical Dyspepsias.

My one criticism is that the book is not sufficiently illustrated.

E. E.

INDEX AND HANDBOOK OF ROENTGEN RAY THERAPY. By DR. ROBERT LENK, Privat-Dozent of Medical Roentgenology, University of Vienna, translated by T. I. CANDY, M.B., B.CH., D.M.R.E., Hon. Radiologist, Royal Gwent Hospital, Newport, Mon. Pp. 119. Oxford University Press, American Branch, 1926. Price, $2.25.

A DISTINCT service has been performed by T. I. Candy for the English-speaking radiologists in his translation of this work.

It epitomizes the technique of the Vienna school under the able direction of Professor Holzknecht. The book is divided into two parts. Part I entitled "General Section" presents the treatment formula and its interpretation while Part II entitled "Special Section" contains an alphabetical arrangement of "The Various Diseases," summarizing—Mode of Action, Prognosis, Treatment Formulæ, Accompanying and Subsequent Effects; Adjuvant Treatment and Contraindications.

P. S.

CHARLES WHITE, OF MANCHESTER (1728–1813), AND THE ARREST OF PUERPERAL FEVER. By J. GEORGE ADAMI, C.B.E., M.D., F.R.S. Pp. 142; 2 illustrations. New York: Paul B. Hoeber, Inc., 1923. Price, $2.00.

IN this first Lloyd Roberts Lecture of the Manchester Royal Infirmary, the author has told the story of Charles White's methods for arresting puerperal fever. His essay is followed by a reprint of the first edition of White's writings, together with the appendix from the second edition. While perusal of both parts indicate that White's methods were undoubtedly effective, his belief that the disease was due to the absorption of excrementitious matter hardly warrants one in considering him a pioneer in establishing the true nature of puerperal fever. In opposing Semmelweiss' priority in this regard, the author disposes of two of the earliest proponents of its contagiousness (Gordon, of Aberdeen, 1795, and O. W. Holmes, 1843) in six lines. An impartial discussion of this topic would have added considerably to the value of this already valuable book.

E. K.

SKETCH OF THE HISTORY OF THE MAYO CLINIC AND THE MAYO FOUNDATION. Pp. 185; 17 illustrations. Philadelphia: W. B. Saunders Company, 1926. Price, $3.50.

BRIEF biographies of the Mayo brothers and their parents are followed by detailed descriptions of the development of the clinic and its present organization and relation to the various hospitals and the University of Minnesota. While of interest to the many admirers of the Mayo Clinic and perhaps useful to those wishing to follow its lead, the book will also be useful to "some future historian" as a storehouse of facts about the early days of this great clinic.

E. K.

CLINICAL METHODS: A GUIDE TO THE PRACTICAL STUDY OF MEDICINE. By HOBERT HUTCHINSON, M.D., F.R.C.P., Physician to the London Hospital, and HARRY RAINY, M.D., F.R.C.P. (EDIN.), Formerly Physician to the Royal Infirmary, Edinburgh. Eighth edition. Pp. 688; 167 illustrations. New York: P. B. Hoeber, Inc., 1924. Price, $5.00.

A HANDY, useful book, which through numerous editions has been kept up to date by the joint authors. Intended to provide an answer to the question, "How shall I investigate this case?" it furnishes much desirable information in compact space and should be welcomed if not allowed to encroach on the field of the larger and more complete textbooks of medicine and medical diagnosis.

E. K.

SIGNIFICANCE OF PHYSICAL CONSTITUTION IN MENTAL DISEASE. By F. I. WERTHEIMER, Associate in Psychiatry, Henry Phipps Psychiatric Clinic, Johns Hopkins Hospital, and FLORENCE E. HESKETH, Charlton Fellow in Medicine, Johns Hopkins University. Pp. 76; numerous charts, tables and plates. Baltimore: Williams & Wilkins Company, 1926. Price, $2.50.

To a limited extent this subject has long engaged the attention of physicians, but probably more seriously so today than at any time since Lombroso's studies in degeneracy. The important body types observed are asthenic, athletic and pyknic, which last is exemplified in that adventurous, amiable gentleman, Mr. Pickwick. These types are correlated with "constitutional indices," and for this purpose the authors have devised a new anthropometric index based on four measurements, three representing the trunk volume and the other the leg length. The text is not always clear, and there are instances where words are inaptly chosen. N. Y.

ACTION AND USES OF THE SALICYLATES AND CINCHOPHEN IN MEDICINE. Medicine Monographs IX. By P. J. HANZLIK, Professor of Pharmacology, Stanford University, School of Medicine. Pp. 184; 12 figures and 2 tables. Baltimore: Williams & Wilkins Company, 1927. Price, $3.50.

THIS is republished from *Medicine* (1926, vol. 5). It is a comprehensive review of literature dealing with laboratory and clinical work done with these drugs since their introduction. The bibliography lists 739 publications. The book should be useful to any physician and invaluable as a course of reference to original sources for those particularly interested in this subject. C. S.

HYDROGEN-ION CONCENTRATION. VOL. I. PRINCIPLES OF THE THEORY. By LEONOR MICHAELIS, M.D. Translated by WILLIAM A. PERLZWEIG, PHD. Pp. 299; 32 illustrations. Baltimore: Williams & Wilkins Company, 1926. Price, $5.00.

THIS is the first of three volumes in English of the author's well-known German monograph, revised and greatly enlarged, which, when completed will be the most ambitious and important contribution as yet made to the study of the ions in biology. The present volume is concerned with the theory underlying the measurement and behavior of the hydrogen and other ions in simple and complex systems as factors in various chemical equilibria and also as sources of potential differences. It is with notable skill that the author clarifies this concededly difficult subject, while at the same time keeping it within the grasp of the reader possessing only an ordinary mathematical equipment, yet this is accomplished by careful and thorough explanation combined with the author's ability for logical treatment.

Great praise is due the translator for undertaking the translation of so valuable a book, as well as for the excellent manner of its accomplishment. J. R.

LECTURES ON NUTRITION: A SERIES OF LECTURES GIVEN AT THE MAYO FOUNDATION AND AT THE UNIVERSITIES OF WISCONSIN, MINNESOTA, NEBRASKA, IOWA AND WASHINGTON (ST. LOUIS). Pp. 243. Philadelphia: W. B. Saunders Company, 1925.

THIS series of six lectures given under the auspices of the Mayo Foundation, dealing with the more recent developments in the study of metabolism, make an unusually fascinating group of scientific short stories. Although they are essentially reviews, there is

included much that is new and in many cases original with the speakers. The fact that the lectures are given by F. G. Benedict, Graham Lusk, E. F. Du Bois, A. V. Hill, E. V. McCollum and H. M. Evans makes further comment unnecessary. J. R.

DAS AUTONOME NERVENSYSTEM. By ERICH SCHILF, Privatdozent für Physiologie, Assistent am physiologischen Institut der Universität Berlin. Pp. 207; 25 illustrations. Leipzig: George Thieme, 1926.

A VERY excellent summary of what is known today in the realm of the vegetative nervous system. The subject is taken up in a very systematic manner. The book has two major divisions: (1) A general discussion; (2) special part. Under the former there is a consideration of the sympathetic division, the parasympathetics, the peripherally placed ganglia and the tissue innervated by this system. Under the second division is discussed the innervation of the heart, vessels, tracheal and bronchial muscles, the vasodilator sympathetic and parasympathetic nerves, the capillaries, the veins and, finally, a general consideration of the supply of the individual organs with nerves to their vessels. The literature is extensively quoted. While little that is new is brought out, it is a welcome compilation of a subject that is still in darkness. N. W.

ENZYMES, PROPERTIES, DISTRIBUTION, METHODS AND APPLICATIONS. By SELMAN A. WAKSMAN and WILBURT C. DAVISON; New Jersey Agricultural Experiment Station and Johns Hopkins Hospital. Pp. 363. Baltimore: Williams & Wilkins Company, 1926. Price, $5.50.

A VERY complete book on the study of enzyme reaction with a bibliography of 1323 references. It is divided into four sections as the title indicates. Its particular value over other books on enzyme study is its completeness and its emphasis on the practical applications and preparations of different enzymes. It is a very useful book as a reference whenever any study of enzyme action is undertaken. W. K.

THOUGHT AND THE BRAIN. By HENRI PIÉRON, Professor at the Collège de France. Translation. Pp. 262, 20 illustrations. New York: Harcourt, Brace & Company, Inc., 1927, Price, $4.00.

THIS interesting volume contains a comprehensive discussion of aphasia, war contributions to neurology, and La Picques' chronary

theory dealing with the duration of electrical excitation in a motor nerve or muscle and its bearing upon the specificity of nervous impulses.

It is inferred that some form of thought is shown in the lower species, for example, the devil-fish, bee and ant, so that "they profit by experience and adapt their behavior to circumstances." Of course if they did otherwise they would perish. N. Y.

THE TREATMENT OF CHRONIC ARTHRITIS AND RHEUMATISM. By H. WARREN CROWE, D.M., B.CH. (OXON.), M.R.C.S., L.R.C.P. Pp. 196, 16 illustrations and 2 charts. New York: Oxford University Press, American Branch, 1926.

THIS volume deals with the practical application of vaccine therapy in arthritis and nonarticular rheumatic disease. The author believes that vaccine is the ideal agent for the treatment of these conditions and that failures in its use are due to faulty methods of selection or preparation of the vaccine, and particularly to improper dosage or faulty timing of the dose interval.

The dangers of overdosage are stressed and an attempt is made to differentiate between relapse under treatment and the development of vaccine sensitiveness. A number of illustrative cases are cited. This book gives evidence of wide experience and careful observation on the part of the author, his deductions are interesting, and the subject of vaccine therapy is treated at length and in a novel and most interesting manner. R. T.

CHRONIC RHEUMATIC DISEASES. THEIR DIAGNOSIS AND TREATMENT. By F. G. THOMSON, M.A. (CANTAB.,) M.D., F.R.C.P., LONDON, Physician to the Royal United Hospital, Bath; Consulting Physician to the Royal Mineral Water Hospital, Bath, etc., and R. G. GORDON, M.D., D.SC., M.R.C.P. (EDIN.), Physician to the Royal Mineral Water Hospital, Bath, and to the Children's Orthopedic Hospital, Bath; Assistant Physician to the Royal United Hospital, Bath. Pp. 202. New York: Oxford University Press, American Branch, 1926. Price, $2.75.

THIS volume presents a series of chapters descriptive of various types of rheumatic disease and chronic arthritis. Fibrositis, climacteric arthritis, intercostal neuralgia, lumbago and sciatica are each awarded a chapter.

In the first part of the book the clinical aspect of the disease is described and diagnosis and treatment discussed under each head-

ing. A second part deals briefly with certain difficulties of diagnosis and the third part with general principles of treatment, climate, physiotherapy, hydrotherapeutic methods, etc., are discussed.

This book contains little that is novel, but does call attention to certain so-called rheumatic manifestations which are frequently overlooked. R. T.

ESSAYS IN THE HISTORY OF MEDICINE. By KARL SUDHOFF, M.D., Professor of History of Medicine in the University of Leipzig, 1895–1924. Translated by various hands and edited, with foreword and biographic sketch by FIELDING H. GARRISON, M.D., Lieutenant Colonel, Medical Corps, U. S. Army. Pp. 397; 7 illustrations. New York: Medical Life Press, 1926. Price, $5.00.

THE author's preëminent position in the field of medical history is enough to guarantee the value of the present volume, even though the volume contains only such short studies as he pubished under the modest title, sketches. These have been artistically translated by a group of translators between whom no comparisons can be drawn. The volume is not only delightful reading but a valuable reference book for all interested in the development of medicine and its history. O. P.

BOOKS RECEIVED.

Abstracts of Theses. The University of Chicago Science Series, Vol. III, 1924–1925. Pp. 351. Chicago: University of Chicago Press, 1927. Price, $3.00.

A Textbook of Medicine. By ONE HUNDRED AND THIRTY AMERICAN AUTHORS. Edited by RUSSELL L. CECIL, M.D. Pp. 1500; 29 illustrations. Philadelphia: W. B. Saunders Company, 1927. Price $9.00. (To be reviewed later.)

Malarial Psychoses and Neuroses. By WILLIAM ANDERSON, M.D., F.R.F.P.S. (GLAS.). Pp. 395; 18 illustrations. New York: Oxford University Press, American Branch, 1927. (To be reviewed later.)

Adapted Group Gymnastics. By LILLIAN CURTIS DREW. Pp. 150; 14 illustrations. Philadelphia: Lea & Febiger, 1927. Price, $1.75. (To be reviewed later.)

International Medical Annual for 1927. Pp. 560; 158 illustrations. New York: William Wood & Co., 1927. Price, $6.00. (To be reviewed later.)

Postencephalitic Respiratory Disorders. By SMITH ELY JELLIFFE, M.D., PH.D. Pp. 135; illustrated. New York: Nervous and Mental Disease Publishing Company, 1927. Price, $2.50. (To be reviewed later.)

Medical Clinics of North America. Boston Number, March, 1927. Pp. 311; 34 illustrations. Philadelphia: W. B. Saunders Company, 1927.

Birth Injuries of the Central Nervous System. Medicine Monographs XI. Pp. 164; 56 illustrations. Baltimore: Williams & Wilkins Company, 1927. Price, $4.00. (To be reviewed later.)

A Textbook of Organic Chemistry for Students of Medicine. By HUGH C. MULDOON, D.Sc. Pp. 496, 32 illustrations. Philadelphia: P. Blakiston's Son & Co., 1927. An elementary textbook satisfactorily planned to meet the need of students preparing for medicine, pharmacy or dentistry.

The Normal Chest of the Adult and the Child. By J. A. MYERS. Pp. 419; 141 illustrations. Baltimore: Williams & Wilkins Company, 1927. Price, $5.00. (To be reviewed later.)

A Manual of Gynecology. By JOHN OSBORN POLAK, M.SC., M.D., F.A.C.S., 3d edition. Pp. 402; 157 illustrations. Philadelphia: Lea & Febiger, 1927. Price, $5.00. (To be reviewed later.)

Intracranial Tumors. By SIR JAMES PURVES-STEWART, K.C.M.G., C.B., M.D. (EDIN.) Pp. 206; 72 illustrations. New York: Oxford University Press, American Branch, 1927. (To be reviewed later.)

Should We Be Vaccinated? By BERNHARD J. STERN. Pp. 146. New York: Harper & Brothers, 1927. Price, $1.50.

Diseases of the Skin and Syphilis. By ALBERT STRICKLER, M.D. Pp. 689; 218 illustrations Philadelphia: F. A. Davis Company, 1927. (To be reviewed later.)

Tiger Trails in Southern Asia. By RICHARD L. SUTTON, M.D., ScD., LL.D., F.R.S. (EDIN.) Pp. 207; 115 illustrations. St. Louis: C. V. Mosby Company, 1927. Price, $2.25. (To be reviewed later.)

Transactions of the American Surgical Association, 1926. Pp. 632; illustrated. Philadelphia: William J. Dornan, 1927.

A Handbook of Diseases of the Stomach. By STANLEY WYARD, M.D., B.S., M.R.C.P. Pp. 387; 32 illustrations. New York: Oxford University Press, American Branch, 1927. (To be reviewed later.)

Die Klinik der bösartigen Geschwülste. Vol. I and II, 1924–1925. By P. ZWEIFEL and E. PAYR. Pp. 860 and 740; 242 and 266 illustrations. Leipzig: S. Hirzel, 1927. (To be reviewed later.)

PROGRESS

OF

MEDICAL SCIENCE

MEDICINE

UNDER THE CHARGE OF

W. S. THAYER, M.D.,

PROFESSOR OF MEDICINE, JOHNS HOPKINS UNIVERSITY, BALTIMORE, MARYLAND,

AND

JOHN H. MUSSER, M.D.,

PROFESSOR OF MEDICINE, TULANE UNIVERSITY OF LOUISIANA, NEW ORLEANS.

Ephedrin: A Clinical Study.—William S. Middleton and K. K. Chen (*Arch. Int. Med.*, 1927, **39**, 385) have studied the effect of this drug, ephedrin, on 41 patients. Clinical studies include the effect upon the blood pressure, results of treatment of a group of 25 patients with asthma, and ophthalmological studies. The authors found that the drug in varying doses caused an average rise of systolic blood pressure of 28.5 mm. of mercury, a rise which lasts for at least five hours and which is not accompanied by a corresponding diastolic rise. In some cases the rise of systolic pressure was accompanied by a corresponding rise in the pulse rate, while in other cases the rise of pressure was not associated with any increase in the heart rate—rather a diminution. The rise in the blood pressure did not seem to be effected by the heart rate. Larger doses than are usually given clinically were accompanied by subjective and objective signs such as sweating, tremor, tonal arrhythmia, extrasystoles, palpation and weakness, a feeling of warmth, chilly sensation, nausea, vomiting and dizziness. In 25 patients with bronchial asthma, ephedrin controlled the attacks in 9 instances, caused improvement in 8 and showed inconclusive negative results in the other 8. In hayfever ephedrin has been particularly successful. In fact, it is in this condition and in asthma that the internist has found the drug of value. The authors do not report upon any cases of hayfever.

The Acoustics of the Bronchial Breath Sounds: Application to Phenomena of Auscultation as Heard in Lobar Pneumonia.—It is rather refreshing in these days of laboratory predominance in diagnosis to

read a paper devoted to some of the phenomena that are found on physical examination, many of the findings of which are considered as proven without question. GEORGE FAHR (*Arch. Int. Med.*, 1927, **39**, 286) has investigated physical signs that are heard on auscultation of the lung in pneumonia. He gives a detailed discussion of the mechanism of production of these sounds. That bronchial breath sounds be produced, it is necessary that the solidification reach to bronchi at least 2 mm. in diameter. These bronchi are usually 3 cm. from the pleural surface in the upper lobes and 5 cm. in the lower lobes. It thus seems that bronchial breathing cannot be produced unless there is a relatively pronounced area of solidification, tending to show that small areas of bronchial breathing throughout the chest of an individual with bronchopneumonia exist only in the minds of the auditor. Pectoriloquy requires even more pronounced solidification, which must reach bronchi 5 to 6 mm. in diameter before this particular physical sign may be elicited. The early chest signs upon physical examination of patients suffering from pneumonia show that on auscultation crepitant râles may be heard, with diminished or absent breath sounds and diminished spoken voice. It is interesting as an aside remark to recall that Laennec laid greater stress on pectoriloquy than any other ausculatory sign, in fact he was unwilling, in the early experiences with his primitive stethoscope, to make a diagnosis of pulmonary tuberculosis unless this sign was present.

SURGERY

UNDER THE CHARGE OF

T. TURNER THOMAS, M.D.,

ASSOCIATE PROFESSOR OF APPLIED ANATOMY IN THE MEDICAL SCHOOL AND ASSOCIATE PROFESSOR OF SURGERY IN THE SCHOOL FOR GRADUATES IN MEDICINE IN THE UNIVERSITY OF PENNSYLVANIA; SURGEON TO THE PHILADELPHIA GENERAL AND NORTHEASTERN HOSPITALS.

Observation on the Surgery of the Large Arteries.—HOLMAN (*Ann. Surg.*, 1927, **85**, 173) says that ligation of one of the large arterial trunks should be accompanied also by occlusion of the accompanying vein. From experimental evidence, a new principle in the simultaneous ligation of artery and vein seems admissible. Under certain circumstances it is preferable to ligate the vein proximal to the site of the arterial ligament, for example, ligation of the popliteal artery should be accompanied by ligation of the common femoral vein above the entrance of the deep femoral and saphenous branches. In the experimental animal, the incidence of gangrene was greatly decreased by the application of this principle. A coarse ligature, such as a broad tape should be applied to the large arterial trunk, rather than fine ligatures, since the latter cut through the arterial wall with distressing rapidity. If feasible, division of an artery between ligatures should supersede

ligation in continuity even of the abdominal aorta, primarily because of the lessened possibility of fatal erosion of the arterial wall. Partially occluding ligatures and crushing ligatures applied to large vessels are both equally and highly dangerous, because of fatal rupture of the wall of the vessel. The ligature should be tied so as to occlude the artery, but not to crush it. Likewise it would seem better not to use a partially coarcting ligature central to a totally occluding one. Proximal ligation of the artery for an arteriovenous fistula is contraindicated not only because of the imminent danger of distant gangrene, but also because it is entirely futile in eliminating the fistula, should gangrene be averted. Following operations upon the large vessels, the wound should be completely closed without drainage.

Diverticulitis.—FIFIELD (*Lancet*, 1927, i, 277) says that diverticula of the large intestine may be congenital or acquired. The commonest site for the acquired variety is the pelvic colon, while above the splenic flexure and in the rectum they are relatively much less frequent. The wall of the diverticulum was composed of mucosa, submucosa and serosa, and in the cases in which it had entered an epiploic appendix, there was a quantity of fat beneath the serosa and it was very easy to overlook the presence of the diverticulum. Abscess formation is more frequent than general peritonitis, the reason being that by the time perforation or penetration occurs, protective adhesions have usually formed, thereby eliminating the suppurative process. Peridiverticulitis is a condition characterized by enormous thickening of the bowel wall, so that it may measure as much as 1 inch from mucosa to serosa. As one would expect in the case of long-standing chronic inflammation, carcinoma may supervene. How frequently this happens is very difficult to say, but in the Mayo Clinic 7 cases out of 27 are reported. The clinical features of acute diverticulitis have been well described as those of acute appendicitis in the left iliac fossa. They included the usual general constitutional disturbance with elevation of temperature, pulse rate, with pain, tenderness and rigidity in the left iliac fossa with or without the presence of a lump. Sometimes these signs and symptoms were in the hypogastrium or right iliac fossa.

Study of Verumontanum.—MCCARTHY, RITTER and KLEMPERER (*J. Urol.*, 1927, **17**, 1) give several short abstracts from the literature to demonstrate the uncertainty existing among the numerous authors and authorities on the anatomy of these parts. Anatomic and histologic studies give explanations of the physiologic fact that the seminal vesicles are distended when solutions are injected either through the vas deferens or ejaculatory ducts, because the normal resistance of the walls of the ejaculatory duct (which lumina become gradually smaller as they approach the urethral floor) causes the liquids to flow toward the seminal vesicles. A large muscular organ (the prostate) surround the ejaculatory duct and offers resistance to their distention. The seminal vesicles are distended when solutions are injected by way of the ejaculatory duct prior to any solution appearing in the vas deferens because the duct of the seminal vesicle is a direct continuation of the ejaculatory duct. The lateral wall of the duct of the seminal vesicle contains elastic tissue and is therefore less resistant and more readily

distended than the ampulla of the vas deferens. The lumen of the ampulla contains several valvelike protecting folds within the lumen, which tend to obstruct the entrance of any fluid into the vas deferens.

Deep Roentgen Therapy in Disease of the Prostate Gland.—LAZARUS (*J. Urol.*, 1927, **17**, 37) states that a most frequent complaint of middle-aged men is some difficulty in the mechanism of urination. It can be stated with certainty that disturbances of micturition in men past forty-five are most frequently due to tumors within the prostate gland and less frequently to prostatitis. Adenoma and carcinoma of the prostate are the tumors most frequently encountered, and of these, the benign neoplasms constitute the largest number. Urinary obstruction in adenoma of the prostate depends to a large extent upon the degree of edema of the mucosa of the prostatic urethra. Congestion and mucous membrane edema are important factors in prostatitis. Roentgen ray therapy is often a valuable palliative measure in the treatment of these conditions. The good effects of Roentgen ray therapy are dependent upon the ability of such radiation to reduce congestion. Roentgen ray does not sterilize an infected prostatic focus. Roentgen ray does not reduce the size of the prostatic tumor. The author does not wish to substitute this process for surgery, but merely brings out that in selected cases Roentgen therapy is distinctly useful in treating hypertrophy of the prostate and cases of prostatitis.

PEDIATRICS

UNDER THE CHARGE OF

THOMPSON S. WESTCOTT, M.D., AND ALVIN E. SIEGEL, M.D.,
OF PHILADELPHIA.

A Survey of the Incidence of Vulvovaginitis in New York City, Etc.—WEHRBEIN (*Am. Pediat.*, 1927, **44**, 243) makes a report of the investigation made by the Committee on Vaginitis. Their results should be of value to all having to deal with large groups of girls. They found they were unable to gather complete statistics on the incidence of gonorrheal vaginitis because reliable figures were not available from the expected sources. This disease is an infection of serious import to female children and occurs with sufficient frequency to be a definite child health problem. The highest incidence and distribution appears to be in homes where filth and unhygienic conditions prevail. No uniform method of treatment has been adopted. Regulations of health departments are not complied with and it seems urgent that stricter enforcement of existing laws relating to this infection be practised. There is difference of opinion among the profession as to the etiology of vulvovaginitis, but there was a unanimity of opinion among the heads of institutions as regards the seriousness of the problem. Every possible safeguard

is employed to keep vaginitis cases out of institutions, for it spreads like wildfire. Direct contact is responsible for a very small percentage of the infection. Because of the danger of the disease spreading, children with vulvovaginitis are denied admission to hospitals for necessary operations and are refused care in orphan and other institutions. This renders a hardship to those children. Most institutions are lacking in provision for caring for this infection both in the acute stage and in convalescence. In New York City it was found that because of the lack of district clinics available for treatment of this condition, that the mother and patient had to travel long distances. The social implications of gonorrheal vaginitis are important and are deserving of vigorous community study. They have been much underrated in the past. The survey showed the need of: (1) Social as well as medical adjustment of the patients; (2) the inclusion of gonorrheal vaginitis in public health programs; (3) increased clinical and convalescent facilities for these patients; (4) separate statistics of gonorrheal vaginitis from those of adult gonorrhea, and (5) scientific bacteriologic and clinical study.

Focal Infection in Children.—MITCHELL (*Atlantic Med. J.*, 1927, **30**, 481) states that the attempt to explain the theory of focal infection has stimulated the ingenuity of its advocates, and has led to reasoning which in some cases is more or less substantiated by facts, or suggested by probability. It is apparent that removal of one demonstrated focus may have no effect if others exist and remain. Foci may readily be multiple and even the presence of one focus perdisposes to others. Any infection in the tonsils and adenoids may encourage disease of the middle ear and nasal sinuses. Likewise a secondary localized abscess may persist in adjacent lymph glands after the primary focus has been removed and likewise diseased teeth may lead to secondary infection of the maxillary sinuses. More or less permanent destructive changes may have taken place in tissue and return to normal, therefore, may be impossible even though the focus of infection is eradicated. This is especially true in regard to the tonsils and adenoids, parts of which are often found after operation. In some individuals infection of the type which may be called focal may exist without evident systemic effect. The presence of pathogenic microörganisms in the body does not always cause disease as there may be a natural or acquired immunity which prevents this. It is probable that a hereditary tendency exists to certain diseases and this must be present in addition to the presence of the exciting or predisposing cause. He feels that there is certainly such a thing as rheumatic diathesis and very possibly others. It may here be necessary to say lowered resistance, either local or general, to assist in the action of focal infection. Areas of focal infection vary in their local condition, so that absorption of bacteria or their products may or may not be possible. In the light of our present knowledge, and from our clinical experience and experimental study there can be no doubt that certain pathologic changes can be cured or improved by eradication of the foci of infection.

Fetal Diphtheria.—TRAUGOTT (*Zentralbl. f. Gynäk.*, 1926, **50**, 3255) reports a case which he believes to be the first in the literature in which

diphtheria was transmitted from the mother to the child *in utero*. This mother, three months pregnant, was taken ill with symptoms of diphtheria and the diagnosis was corroborated by culture of the throat. She was given an injection of serum two days after the onset of the illness which resulted in prompt recovery. The second examination of throat culture, six days after the onset, was negative. Five days later there was a slight rise in temperature and after another six days the patient had a chill followed by a rise of temperature. Thirty days later she was delivered of a newly dead embryo. The mother recovered. Autopsy of the embryo resulted in numerous bacilli resembling diphtheria in morphology, distribution and stain properties from the perineal exudate. Culture of the blood of the umbilical cord was negative. The liver was enlarged, and on its surface were numerous yellowish specks which proved to be nests of bacilli resembling diphtheria bacilli. There was no abnormality of the placenta other than the infarction. The author does not believe that the bacilli passed from the chorion which was healthy and uninjured, but it seems more probable to him that they made their way from the mother's blood into the intervillous space, where they multiplied as on culture medium. The placenta became partly detached either by direct action of the bacteria or from the uterine contractions started up by the mother's illness. From the chorionic vessels thus opened up the bacilli passed into the umbilical vein and were for the most part deposited in the liver. Here their multiplication developed and peritonitis which caused the death of the embryo, followed. The uterine contractions, following the death of the fetus, pressed the bacilli out of the intervillous space back into the circulation of the mother, resulting in chill and fever, but no further development of the infection because of her recent immunization.

Two Cases of Precocious Puberty.—KEATINGE (*J. Obst. and Gynec. British Empire*, 1926, **33**, 653) reported one child who was seven years of age, who had been menstruating regularly for six months. She was well developed. On rectal and abdominal examination a cyst on the left ovary was felt. The uterus was of the adult type, but not enlarged and in good position. This cyst was removed and there was a cessation of menses, and after six months the precocious secondary sex characteristics had disappeared. The other patient was three and a half years of age in whom menstruation began at one month. Pubic hair was present by the end of the first year. The breasts were well formed. A small ovarian cyst was discovered and this with a part of the ovary was removed. In this patient there was no disappearance of the menses nor any change in the sex characteristics.

Tuberculosis in Childhood.—MYERS (*J. Am. Med. Assn.*, 1927, **88**, 1457) indicates that from the standpoint of prevention of tuberculosis, there is no more favorable time in the entire span of life than during the period of childhood. With the infant it is a question of preventing exposure. In a family of some intelligence the prenatal worker can do a great deal by teaching the necessity of having all members of the family examined for tuberculosis. This examination should be allowed and include those, other than members of the family, who will have intimate association with the infant. Teaching of this sort will prevent

a tremendous amount of exposure, and will save the lives of many babies. Next in importance is direction as to the proper food, rest and hygiene for all members of the family. In the period of childhood the problem of preventing exposure is much more difficult and is almost impossible. Many cases of tuberculosis are unsuspected and there are many carriers to whom children are exposed. To offset this the body of a child is better able to resist bacilli than at any other period. This depends upon the structure of the lymph nodes in childhood. Because of the better resistance at this age this is the best period of life to treat tuberculosis in an attempt to prevent the destructive type of the disease which develops in later life. The best means of accomplishing this is in the schools, where all cases of children suffering from tuberculosis of the lymph nodes should be found and placed in special schools, where they can receive the best of attention as regards rest, food and hygiene. They are thus enabled to be closely supervised by physicians, and nurses, and where their relatives can be taught the dangers of the adult type of the disease.

OBSTETRICS

UNDER THE CHARGE OF

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The Obstetric Future of Women Delivered by the Low or Cervical Cesarean Section.—PHANEUF (*Am. J. Obst. and Gynec.*, 1927, **13**, 446) gives a brief history of the low Cesarean section and the efforts of a limited group of operators to rejuvenate this operation. All were well agreed upon the fact that this procedure of keeping the incision low overbalanced the slightly increased technical difficulty necessary in its performance. The claims made for the low or cervical operation are: (1) The cervical area stands infection better and the pelvis is more resistant to infection; (2) the wound is placed in a contractable part of the uterus, and lessens the possibility of rupture in subsequent pregnancies and labors; (3) adhesions are less frequent; (4) a real test of labor may be given after this operation; (5) incision hernias in the abdominal wall are less frequent; (6) the convalescence approached more nearly that of a pelvic delivery; (7) the morbidity and mortality are greatly reduced; (8) it permits the delivery of a living child through the abdomen, where infection exists which would make a classic operation a hazardous undertaking. The article goes into the work done in European as well as American clinics and refers to the results. Three methods of approach of the low section are given: Modified

Sellheim method, the Veit-Fromme-Hirst method and the method of Latzko. The author has substituted the cervical operation for the classic operation since 1909. The question of previous Cesarean section scar and secondary operation is taken up and delivery by the pelvic route following a low Cesarean section. The conclusions drawn are that the healing of the cervical scar is so perfect that it is impossible to locate the previous line of incision. Definite protection against rupture of subsequent pregnancies and labor, delivery through the natural passage is possible. "Once a Cesarean section always a Cesarean section" does not hold good necessarily for this type of operation. The operation may be repeated with ease. No difficulty is encountered in the separation of the bladder. Pelvic adhesions are reduced to a minimum. Abdominal herniæ were not observed in any of these operations. Convalescence was that of a pelvic delivery. The protection against peritonitis is a definite factor in favor of the low or cervical Cesarean section.

Rectal Ether Analgesia in Labor.—A review of 5800 cases, the technique and results at the New York Lying-In Hospital are given by HARRAR (*Am. J. Obst. and Gynec.*, 1927, **13**, 486); it adds another to the series of articles by the author on this subject, in which he claims 85 per cent had great relief from labor pains, a moderate amount of relief in 10 per cent and 4 per cent were negative in result. Labor in multiparæ is often easy and brief, and this method of analgesia is scarcely needed. It is said to be more satisfactory in the primipara cases. The details of the standard technique and the materials used have varied very little in the past two years. The question of the technique of administration is especially stressed as the results depend very materially on its administration. The end results of the properly administered rectal analgesia during labor show that it is a great aid and relief in 85 per cent of cases; that there is no prolongation of the perineal stage or increase in forceps delivery, in asphyxia at birth, or a rise in the still-born rate. The only contraindication given to the procedure is uterine inertia, and the only restriction given is not to start the procedure too soon. Great stress is laid on the time at which this procedure is started. The woman should be in active labor; the pain should be recurring every four to five minutes and lasting forty seconds by the watch; in primiparæ preferably the cervix should have attained a dilatation of two or more fingers. The mechanism and progress of labor must be as closely followed as if no analgesia were employed. The rectal analgesia is safe and effective; it is applicable in the hospital and home confinement; it does not require the services of a trained anesthetist; it is the surest, safest and most effective method for the relief of pain in childbirth that has yet been devised and is without danger to either the mother or her child.

The Details of Postpartum Care.—In this article the entire subject of postpartum care is set forth, and POLAK (*Am. J. Obst. and Gynec.*, 1927, **13**, 432) states that 60 per cent of the lesions which make up the diseases peculiar to women are the direct results of poor obstetrics. Trauma, infection and lack of appreciation of the physiologic process of involution are responsible for a large proportion of these cases.

Better intrapartum and postpartum care is essential and are classed among the functions of the obstetrician. There are two distinct essentials of the care of the obstetrical case: (1) To deliver the woman of a living child with the minimum amount of injury to the birth canal and to her general system; (2) at the completion of the puerperium that the patient be in good physical condition, able to attend her household and social duties. Both of these necessitate the careful antenatal study, watchfulness and observation with intelligent added aids in the first and second stages of labor. The termination of labor after completion of the first stage is of timely use. The postpartum care begins immediately after the completion of the second stage and the management of the third stage is given in detail. Great stress is laid on a scrupulous surgical aseptic technique. The repair of episiotomy and cervical laceration is gone into in detail, the entire puerperal stage, including the exercises shown with diagrams, care of the breast, medication, diet and final examination before discharge from the hospital is taken up. The future health of the individual depends largely upon the recognition of the prenatal study, intrapartum asepsis and intelligent postpartum care. All of these are emphasized and can be easily carried out in carefully studied and guided obstetrical cases.

GYNECOLOGY

UNDER THE CHARGE OF

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Use of Parathyroid Extract in Hemorrhage.—There are many times when we are called upon to treat patients who are suffering from uterine bleeding when a satisfactory hemostatic medicine would be of great assistance. Of course packing the uterus and other surgical measures are quite reliable means of controlling such bleeding but not infrequently for some definite reason it would be preferable if only medical measures were employed. In the past our reliance has been placed in ergot, stypticin, hydrastis and other hemostatic drugs which are often of great value. However, if we can add any other reliable drug to our available agents we should not overlook the opportunity. Of late quite a bit of study has been done on the calcium metabolism in its relation to hemorrhage of all kinds and because the parathyroid glands are supposed to be intimately related to the calcium metabolism, the use of parathyroid extract in the control of hemorrhage has been recently advocated. Some work in this line has been reported by GORDON and CANTAROW (*J. Am. Med. Assn.*, 1927, **88**, 1301) who used parathyroid extract in a series of 347 patients with hemorrhage

from various causes, some of them of uterine origin. They believe that the results are more dependable than with the oral or intravenous administration of calcium and furthermore gastric irritation and other untoward effects are avoided. The most favorable results followed the administration of from 10 to 15 units every thirty-six hours for 1 to 3 doses, while the unfavorable results occurred when overdosage and prolonged administration were employed. This form of therapy is still in the experimental stage but may prove to be of value in selected cases.

Prolapse of Urethra in Children.—According to HEPBURN (*Surg. Gyn. and Obst.*, 1927, **44**, 400) prolapse of the female urethra in children is a true hernia, the result of strain and congenitally poor tissues. The treatment of this condition in the past has been by resection of the prolapsed urethra, a sort of circumcision. As an improved method of treatment, he suggests that the patient be placed in the Trendelenburg position and a midline suprapubic incision made. The bladder is then exposed retroperitoneally and dissected free from its prevesical attachments. When the neck of the bladder is freed enough so that traction on the bladder reduces the prolapse, the anterior bladder wall is sutured to the structures in front of it, usually to the periosteum of the pubic bone and the posterior fascia of the rectus muscle. The wound is then closed around a rubber tissue drain to the prevesical space. The legs should be apart during the operation so that an assistant can report when the prolapse is reduced and whether it stays reduced after the stitches are placed. The patient should be encouraged to void frequently after the operation so that the dilated bladder may not be acted on by any sudden intraäbdominal pressure and the sutures thus torn before the adhesions have thoroughly anchored the bladder.

Formation of Vagina from Meckel's Diverticulum.—In those sad cases in which, owing to a developmental defect there is an absence of the vagina, many operative procedures have been devised for the purpose of forming an artificial vagina. Perhaps the best known and generally most satisfactory operation is that which was described by Baldwin and is named after him. In this operation a loop of the small intestine is isolated from the remainder of the intestinal canal and is pulled down into a space made for the vagina and its lumen serves as the new vaginal canal. As an evidence of the ingenuity which is often displayed by operators who are interested in plastic and restorative surgery, the report of WASSILIEW (*Zentralbl. f. Gynäk.*, 1927, **51**, 806, has an interesting feature, although not of much practical value. In the patient on whom he intended performing the classical Baldwin operation for the formation of an artificial vagina, on opening the abdomen he found a Meckel's diverticulum, which was freely movable except for its insertion into the ileum. Instead of isolation a loop of small bowel, he brought down the diverticulum into the space formed for the vagina and reports a very satisfactory end result. Of course it would be only in the exceptional case where the combination of absent vagina and Meckel's diverticulum was present and even then the preoperative detection of a diverticulum is, to say the least, a rather clever diagnostic feat.

Treatment of Pruritus of the Genitalia.—Itching of the female genitalia is at times one of the most difficult conditions to relieve because there are so many possible etiologic factors. Such cases require very careful study if the basis of it can be found, relief may frequently be obtained. In cases where the causative factor cannot be found, ALDERSON (*California and Western Med.*,1927, **26**, 51) believes that the spells of itching are often started by the presence of rectal, vaginal or skin secretions in the folds of the anal mucosa and skin and therefore a rapidly drying, nonirritating solvent should be of use. If this solvent contains an antipruritic agent it will give relief lasting for several hours. Carbon tetrachlorid containing ½ per cent phenol or 2 per cent camphor has been found very useful. It penetrates the ducts, follicles, crypts and folds in the skin, dissolves secretions and excretions and destroys bacteria and fungi. It dries very quickly but has the objection that its vapor may cause vertigo. This can be guarded against by applying the solution carefully and providing for plenty of ventilation in the room. Sometimes it produces considerable smarting but this lasts only a few seconds and is often welcome to the patient. Usually the application will give relief over night, but the solution should be applied twice daily as a cleanser. After the application a dusting powder such as talc, calomel or magnesium carbonate should be applied.

OTO-RHINO-LARYNGOLOGY

UNDER THE CHARGE OF

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The Diagnosis and Treatment of Laryngeal Tuberculosis.—"There seems to be a general impression that laryngeal tuberculosis is a fatal complication of pulmonary tuberculosis for which little can be done in the way of treatment or care. Such an opinion is entirely erroneous, for no condition responds more rapidly to properly directed treatment than tuberculous laryngitis if a diagnosis is made reasonably early." LOOPER (*Ann. Otol., Rhinol., and Laryngol.*, 1926, **35**, 1041) calls attention to the fact that approximately one-third of all patients with pulmonary tuberculosis have laryngeal involvement and that at autopsy laryngeal lesions can be demonstrated in one-half of the fatal cases. As every person suffering from pulmonary tuberculosis should be considered a potential case for laryngeal complications, it is a mistake to wait for subjective symptoms—huskiness of voice, hoarseness, pain referred to ear or throat, and dysphagia—to develop. It is much better to institute regular, routine laryngeal examinations so that an early diagnosis can be made, thereby affording a better prognosis. The author uses electric cauterization of the local lesion in preference to all other methods.

Pathology of Sphenoethmoidal Sinusitis. — McMahon (*Arch. Otolaryngol.*, 1926, **4**, 310) surveyed 70 cases of chronic hyperplastic sphenoethmoidal sinusitis in order to determine whether or not there was any relationship between the symptoms and the microscopic pathology, and between the microscopic pathology and the end results of the operations. Histopathologic study of the epithelium revealed such changes as thickening, sloughing, polypoid degeneration and metaplasia. In some instances thickening was found in the basement membrane and periosteum, whereas the tunica propria showed edema, round-cell infiltration, fibrosis, dilatation or compression of glands or thickening of bloodvessel walls. In the bone, osteoblastic and osteoclastic activity was noted, as were fibrosis, hyperostosis, osteomalacia and necrosis. Such symptoms as headache, anteronasal discharge, postnasal discharge, asthma, arthritis, failing vision, impaired hearing, and herpes of the second division of the fifth nerve were encountered in the cases studied. The author could find no direct interrelation of the individual microscopic findings, symptoms and operative end results. The incidence of sphenoethmoidal sinusitis was less among men than women, in whom the percentage of good results was much higher. He concludes that "chronic hyperplastic sphenoethmoid sinusitis is a distinct clinical entity in which the operative results are attended with a high percentage of improvement or complete recovery (74.3 per cent)."

The Tampon Treatment of Ethmoiditis.—Stating that "the proper use of nasal tampons makes possible cure in many intractable cases of sinusitis and enhances the likelihood of success after appropriate surgery has proven a disappointment." Dowling (*J. Ophthalmol., Otol. and Laryngol.*, 1927, **31**, 53) describes his method of introducing colloidal silver (in the form of 10 per cent argyrol). The tampon is made by folding sterile long-fiber cotton around a long, thin, wire-like applicator. After saturation by immersion in the argyrol solution, the tampon is introduced into the naris above the scroll of the middle turbinate, first directing it in the direction of the ostium of the sphenoidal sinus, and pushing it as far back as possible between the turbinated bone and the septum. When the applicator has been sufficiently withdrawn in a rotary fashion, the handle is depressed and a final push engages the tampon in the vicinity of the infundibulum—after which the applicator is withdrawn. Tampons should be placed in both nostrils. The use of cocain before placing the tampons is seldom required and should be avoided if possible as best results are obtained without its preliminary use. The tampons should be allowed to remain in the nose from ten minutes to one hour. The author advises that the nares be irrigated after the argyrol-soaked cotton has been removed. He admonishes against a nebulizing oil afterward, as well as irrigation of the nose in women at or about the time of the menses. He says that this method of tamponade is especially valuable in all varieties of ethmoiditis, that the need of ethmoid surgery is lessened to a great degree after a course of tampon treatment, and that his method is applicable to children with ethmoiditis. He concludes that the tampon treatment is not a "cure-all" for ethmoiditis or other sinus disease and that the accessibility of the middle meati, to a large extent, governs its efficacy.

The Voice Test of Hearing.—In a most comprehensive manner, MACFARLAN (*Arch. Otolaryngol.*, 1927, **5**, 1) discusses the psychologic, physical, technical and practical phases of the human voice as an agent for testing hearing. Since so many variables in the voice test have been cited he feels that its merits must be overshadowed by its faults. The chief difficulty is in the inability to produce a dependable, standard and ponderable stimulus by voice. As the voice is a complex of pitches and amplitudes—and consequently of intensities—this is impossible. The voice, as a test instrument, is limited to the field of 300 to 3000 double vibrations. Inasmuch as the pathologic changes of hearing, so far as deafness is concerned, lie most demonstrably at hearing limits above and below this field, other tests are better for determining the degree of deafness at the upper and lower extremes of hearing. Greater care in technique must be exercised with the voice than with any other hearing test. As it is impossible to fix a standard voice stimulus, it is obviously unsatisfactory to report results in terms of hearing distance. If voice hearing is to be reported as to distance heard, it is imperative that the normal hearing distance be noted for the stimulus used. When testing the simpler sensory phenomena of hearing, it is most important to use care in recognizing, in valuing, in excluding, in minimizing and in standardizing the higher mental factors, such as attention, alertness, anticipation, ardor, distraction, indifference, fatigue, memory, training and general intelligence. With care in technique, the voice test can be put to its greatest use in testing speech interpretation. The author believes "that it is reasonable to retain the test in spite of its variables, for as speech hearing is the most important function of the ear, and as the voice test uses as its hearing stimulus the very thing which is most important to test, one is dealing with a direct method. The voice test then would seem to resolve itself into a rough test for speech-hearing distance, and into the most valuable test for speech interpretation."

RADIOLOGY

UNDER THE CHARGE OF
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Exostosis.—MYERDING (*Radiology*, 1927, **8**, 282) groups exostoses with the benign osteochondromas, which, depending on the relative content of bone and cartilage, may be classified otherwise as osteoma, chondroma, fibroma, osteochondrofibroma and osteochondrofibromyxoma. The author has had opportunity to observe 265 cases at the Mayo Clinic, all of which were examined with the Roentgen ray and operated upon. About two-thirds of the cases were in males; the average age was twenty-six years, the youngest being five and the

oldest sixty-four years of age. Roentgenographic characteristics of exostosis are: (1) The cortical point of origin is usually on the diaphysis near the epiphyseal line, and most commonly at the lower end of the femur and the upper end of the tibia and humerus; (2) the base may be narrow or broad; (3) the cortex of the bone may appear to be continuous with that of the tumor (medullary bone is often continued into it); (4) the mass frequently has a cartilaginous cap surmounting it, and it often has a cauliflower-like appearance; (5) a bursa covers the well-developed tumors, permitting the soft tissues to be moved without pain; trauma causing hemorrhage, or infection, may result in swelling visible in the roentgenogram; (6) there is no invasion but rather penetration of tissue; (7) the periosteum is expanded over the tumor but is otherwise normal; (8) the tumor is usually inclined away from the joint. Treatment is surgical, but operation is not always indicated. Recurrence took place in 10 per cent of this series.

Alimentary Tract of Medical Students.—Todd (*Am. J. Roentgenol. and Rad. Therap.*, 1927, **17**, 305) by roentgenoscopic studies has found in young male students that all parts of the alimentary tract are exceedingly sensitive to emotional or nervous conditions. These influence different parts of the tract in various ways. The stomach becomes atonic in outline but not in movement or emptying time. The duodenum shows pseudostasis. Spasm of the transverse colon may inhibit onward movement. The normal position of the small bowel, whether the subject is standing or recumbent, is in the lower abdomen and true pelvis, and it is disposed into ladder-like coils.

Ultraviolet Light in the Treatment of Leg Ulcers.—Schiller (*Arch. Phys. Ther., X-ray, Rad.*, 1927, **8**, 61) has derived the greatest success from the following method: The ulcer is cleansed the day before with boric acid or Dakin's solution. The edges of the ulcer are denuded by brushing with gauze, or by curetting, and the area is then painted with a 2 to 5 per cent solution of mercurochrome. The Kromayer lamp, using either direct pressure or a 1-inch distance, and from three to five minutes time, is then applied. At the same time the body generally is exposed to a therapeutic dose of air-cooled ultraviolet light. After the ulcers have healed care is necessary to prevent recurrence.

Radium Treatment of Hemangiomas.—Andren (*Acta Radiol.*, 1927, **8**, 1) reports the results in 288 cases of hemangioma, 11 of lymphangioma and 69 cases of epidermal nevi. Radium was applied in less than the erythema dose at long intervals. Andren's report indicates very good results. He points out, however, that for perfect cosmetic restoration treatment must be begun within the first year of life; otherwise atrophic scars or "checking" are likely to supervene.

Effect of Diathermy on Gastric Acidity.—By experiments on dogs, Brody (*Arch. Phys. Ther., X-ray, Rad.*, 1927, **8**, 116) has found that subjection of the stomach at frequent intervals to low milliamperage with medium voltage over a long period of time tends to increase gastric acidity both free and total. When the gastric mucosa is

diseased there is an increase of acidity with a return to normal shortly after. Low voltage cannot be used because of its injurious effects. Higher milliamperage with medium voltage increases the acidity, followed by a period of depression and again by a rise. His experiments suggest that this method may be applicable to the treatment of gastric achylias of neurogenic or idiopathic origin.

Ultraviolet Light in Skin Diseases.—ZEISLER (*Arch. Phys. Ther., X-ray, Rad.*, 1927, **8**, 101) concludes from his experience that ultraviolet light is a useful auxiliary in the treatment of many cutaneous disorders, but rarely suffices alone for cure. When properly combined with other remedial agents the light is of value in pyodermias, psoriasis, some forms of eczema, lichen simplex, alopecia areata and acne rosacea. It is of use in cutaneous tuberculosis, but inferior to the Finsen light. He takes a conservative view of the value of violet light in lupus erythematosus, nevus vasculosus, acne vulgaris and alopecia prematura.

Dangers of Introducing Iodized Oil into the Tracheobronchial System.—Lipiodol has of late been extensively exploited for roentgenologic examination of the bronchi. ARCHIBALD and BROWN (*J. Am. Med. Assn.*, 1927, **88**, 1310) have thoroughly reviewed the literature and report 3 cases of their own to show that the proceeding is devoid of danger. One of their patients, who had tuberculosis, died five days after injection. There are numerous other contraindications to the use of lipiodol, including hemoptysis and anaërobic infections, and some writers have advised against the employment of this drug in cases of bronchiectasis, on the ground that it is likely to cause local inflammatory reactions, retention of infectious material, or mechanical reduction of the vital capacity.

NEUROLOGY AND PSYCHIATRY

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Adhesive Spinal Arachnoiditis Simulating Spinal-cord Tumor.—STOOKEY (*Arch. Neurol. and Psychiat.*, 1927, **17**, 151) claims that adhesive spinal arachnoiditis gives rise to spinal cord signs frequently difficult to differentiate from those produced by spinal-cord tumors. The etiology is relatively obscure but the author believes that meningeal infections may be important factors. It is also suggested that the slow insidious trauma resulting from interference with the dorsal and ventral movements of the cord during respiration may result in interference

with spinal-cord conduction. The clinical features in these cases differentiating them from spinal-cord tumors are: (1) The longer duration of and the slow progress in the manifestation of symptoms; (2) complete or partial block as shown by manometric examination of the spinal fluid; (3) the absence of xanthochomia with no increase in the total protein content. Obstruction produced by adhesions does not give rise to venous stasis and hence the suggestion that increased protein content as seen in tumors may be due to interference with venous circulation with diapedesis.

Inadequate Childhood Training, a Factor in Mental Disease.—In considering the so-called functional group comprising more than 50 per cent of the cases of mental illness, BELLINGER (*The Psychiatric Quarterly*, 1927, **1**, 96) believes that the antisocial reactions of many of the nonorganic mental disorders are secondary to defects of personality. However, he does not believe that heredity, focal infections and endocrine disturbances should be overlooked as possible etiologic factors. The schizoid, syntoid and psychopathic types of personality were found to predominate in those individuals developing dementia præcox, manic-depressive reactions and psychoses respectively. In a majority of the cases, the personality of the individuals had been so molded by the family situation and faulty childhood training, that they were unable to adapt themselves to the demands of society. Four case reports are given and a plea made for adequate childhood training to be brought about by education through the professional schools and members of the various professions.

Involvement of Central Nervous System Secondary to Primary Carcinoma of Lung.—PARKER (*Arch. Neurol. and Psychiat.*, 1927, **17**, 198) states that in 4 cases of primary carcinoma of the lung with metastasis in the brain, meninges, spine and nerve roots, practically all the symptoms were due to involvement of the nervous system. In 2 of the cases, the earliest symptoms were headache and vomiting and in the other 2 cases, root pains. In each case the symptoms were variable and the diagnosis difficult. Because of this, the author advocates a complete and thorough physical examination in all cases of disease of the central nervous system.

Some Results of a Second Induction of Malaria in General Paralysis of the Insane.—NICOLE and STEEL (*J. Neurol. and Psychopath.*, 1927, **7**, 208), in a series of 25 cases, all of which showed an insufficient improvement following the first attack of malaria and in which the physical condition was good, found that 20 were successfully reinoculated following a total of 52 inoculations. In only 5 cases was the routine inoculation with infected blood successful. Three "resistant" cases were exposed to mosquito infection. Two of these developed true malaria and one of these acted as donor to other "resistant" patients. The average length of time between the initial and second attack of malaria was seventeen months in each case. Five of the above cases showed marked mental, physical and serologic improvement and 7 more showed slight improvement either mentally or physically. Of the remaining 8, 1 died and the others have showed no improvement.

PATHOLOGY AND BACTERIOLOGY

UNDER THE CHARGE OF
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Neuroblastoma of Adrenal Gland.—The number of cases of this type of tumor is increasing year by year, and the clinical picture is becoming better recognized so that its discovery is not alone an autopsy finding. LEDERER (*J. Cancer Research*, 1926, **10**, 377) reported a case in a child of four years which showed the accepted clinical characters to make a diagnosis during life. Swellings developed on the left side of the head, and the left eye became prominent. By Roentgen ray examination the tumor was recognized in the left side of the abdomen. The proptosis became more marked and the masses in the skull appeared to increase. At autopsy a lobulated tumor mass 11.5 cm. in diameter occupied the left adrenal. The tumor was quite circumscribed and did not invade the kidney or other neighboring organs. It was made up of a delicate stroma in which there were large polygonal cells like ganglion cells, as well as smaller ones. The tumors of the skull and left orbit were entirely composed of small spindle cells in which a few rosettes were seen, there was no evidence that a metastases of ganglion cells had occurred. The invasion of the skull appeared to have developed from the implantation of tumor masses into the dura. It is peculiar that these tumors distribute their metastases to the same side of the body in which the primary arises.

Types of Bacilli in Human Tuberculosis.—RABINOWITCH (*Am. Rev. Tuberc.*, 1927, **15**, 225) concludes that all three types of tubercle bacilli are pathogenic for man. Pulmonary tuberculosis is invariably always caused by the human strain. The bovine strain plays an important röle in human infection, particularly in childhood. There are about 20 cases of avian tuberculosis reported in the literature. A strict division of type is not always possible, as there are several intermediate strains. The author reports a case of dermatomyocitis recurrens, in which she isolated an attentuated bovine strain from the associated pulmonary and intestinal lesions, and an avian strain from the skin lesion.

Remarks on Atypical Forms of Tubercle Bacilli.—PRIBRAM (*Am. Rev. Tuberc.*, 1927, **15**, 235) states that Ferran assumes that the biology and morphology of the tubercle bacillus may vary considerably. He identifies the alpha, beta, gamma, delta and epsilon types. The epsilon

strain sometimes loses its acid-fastness. This is a gradual variation in the properties of the B. tuberculosis. In other cultures Ferran noticed a sudden loss of both the typical growth and acid resistance. These cultures (Delta and Epsilon) may become transmuted into forms with Much granules. According to Ferran's theory there were two qualities of the tubercle bacillus (a) the toxic quality, producing fever and wasting, (b) the quality giving rise to comparatively harmless tubercle formation. The author believes that the tubercle bacillus is a transmutation type lying between the genus bacterium and hyphomyces. It is stated that the tubercle bacillus is closely related to the actinomyces. According to Libman and Newmann, both belong to the group of mycobacterium.

Concerning Aneurysms. — In a general address upon aneurysms KLOTZ (*University of Toronto Studies, Pathological Series*, Number 7, 1926) covers the subject both from the historical and scientific aspects. The aneurysms which were described in the pre-Columbian period were for the most part of traumatic origin, and arose upon the exposed arteries. This type of aneurysm is not as commonly encountered in modern times, but its place has been taken by internal aneurysms which were first described by Paré, after the intensive epidemic of syphilis which swept over Europe in the first half of the sixteenth century. The modern studies on aneurysm began with the careful analysis by Heller and his students. Syphilis receives first place in the development of aneurysm at the present time, but it is noted that with the more intensive treatment of the disease that these tertiary lesions are less frequent. It is pointed out that syphilitic aneurysms still possess an infecting agent in the untreated cases. The virus is not readily demonstrated in the wall of the aneurysm itself, but is more readily found in the peripheral and advancing borders. Aneurysms resulting from acute infections, trauma and war wounds and arteriosclerosis are also discussed in this paper. Attention is attracted to the presence of aneurysms arising spontaneously in animals.

HYGIENE AND PUBLIC HEALTH

UNDER THE CHARGE OF

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Experimental Epidemiology of Tuberculosis.—PERLA (*J. Exper. Med.*, 1927, **45**, 209) found that normal guinea pigs to tuberculous cage mates infected intraperitoneally and with no cutaneous ulceration readily

contract spontaneous tuberculosis. The incidence of spontaneous tuberculosis increases with the intensity and with the duration of exposure. Spontaneous tuberculosis acquired from infected cage mates has with few exceptions the characters of an infection which has entered by way of the digestive tract, disease of mesenteric and cervical lymph nodes being conspicuous. Guinea pigs exposed to tuberculous animals in the same room but not in the same cage may acquire tuberculosis which has the characters of a bronchiogenic infection associated with lesions of the lungs and tracheobronchial lymph nodes.

The Bactericidal Property of Cow's Milk.—JONES and LITTLE (*J. Exper. Med.*, 1927, **45**, 319) tested the bactericidal activity of fresh, raw milk from a number of cows with the nonhemolytic mastitis streptococcus. By using this organism and other means they were able to rule out the action of agglutinin. They state that the milk of all cows examined inhibited the growth of the streptococcus for definite periods. The length of the inhibition varied; the milk from some cows prevented growth for eight hours, that of others for only four or six hours. The inhibitory action may be as strong in the milk of a young cow in its first lactation period as in that of an old cow known to be resistant to udder infection. It is possible to absorb the streptococcus inhibitory substance by first inoculating the milk with Bacillus bovisepticus. The authors were unable to show that the substance was increased by artificial immunization of cows with the streptococcus. Whey obtained by the action of sterile rennet solution inhibited the growth of the streptococcus to about the same extent as the milk from which it was obtained. The authors infer that the substance originates in the udder since it differs from blood alexin in its resistance to heat; it is not increased in the whey, although the blood proteins are more concentrated, and it is not increased in the milk when the cows are artificially immunized or repeatedly exposed to natural infection.

Paris Green Applied by Airplane in the Control of Anopheles Production.—WILLIAMS and COOK (*Pub. Health Rep.*, 1927, **42**, 459) give a description of the encampment of the U. S. Marine Corps at Quantico, Va., and discuss fully the problem of mosquito and larvæ destruction. Paris green, mixed with an inert powder (lime or soap stone) was distributed by an especially equipped airplane. The results were very satisfactory. The amount of Paris green required was about 1 pound per acre of swampy land covered.

Sterilizing Efficiency of Arsphenamin, Neoarsphenamin and Sulpharsphenamin in Experimental Syphilis.—VOEGTLIN and DYER (*Pub. Health Rep.*, 1927, **42**, 176) discuss previous work on the subject, present their own data, and reach the following conclusions: "Sterilization of syphilitic rabbits late in the disease can be accomplished by means of a single large dose of either arsphenamin, neoarsphenamin or sulpharsphenamin. The sterilizing efficiency increases with an increase in the dose and does not decline when the minimal sterilizing dose is exceeded. The data, therefore, indicate the advisability of intensive treatment and contradict the view that intensive treatment interferes with sterilization on account of its alleged interference with immunity

reactions. The minimal sterilizing dose of arsphenamin, neoarsphenamin and sulpharsphenamin is identical in terms of absolute amount of arsenic. The intramuscular injection of sulpharsphenamin is just as effective as the same amount of arsenic in the form of arsphenamin or neoarsphenamin injected intravenously. The 'index of sterilization' —that is, the ratio of maximal tolerated dose to minimal sterilizing dose—is most favorable in the case of sulpharsphenamin, less so with neoarsphenamin and least with arsphenamin. A modification of the tissue transfer test is described, which increases the reliability of this method as a criterion of sterilization from treatment with these drugs."

The Persistence of Streptococcus Scarlatinæ in the Throat of Convalescent Scarlet Fever Patients.—In the 40 cases studied by NICHOLLS (*Am. J. Hyg.*, 1927, **7**, 84) Streptococcus scarlatinæ was found in the throat cultures at the end of the third week in every case. There seemed to be little diminution in the degree of throat infection, as determined by the amount of growth up to the end of the third week, irrespective of the severity of the case, the use of antitoxin, or the presence of complications. All strains isolated at the end of the third week were potent toxin producers. So few cases were studied at the fourth and fifth weeks that no conclusions can be drawn as to the frequency of positive findings at these periods. The author concludes from her findings that patients convalescent from scarlet fever are still infectious three weeks after onset of the disease, and that the three weeks period of isolation customary in Connecticut should be prolonged.

Bacterium Pneumosintes in Clinical Influenza in New York City in 1926—GATES (*J. Exper. Med.*, 1926, **44**, 787) has demonstrated the presence of Bacterium pneumosintes in nasopharyngeal washings from 2 patients in a sporadic outbreak of clinical influenza in New York City in March, 1926. Two strains of bacteria morphologically similar to Bacterium pneumosintes, but differing in certain cultural characters, and 2 others anaërobic filter-passing organisms were also isolated from the 9 patients examined. The blood serum of 16 among 17 persons convalescent from clinical influenza, and of 6 among 10 supposedly normal persons agglutinated 1 or more strains of Bacterium pneumosintes.

Prevention of Measles by Immune Goat Serum.—TUNNICLIFF and HOYNE (*J. Am. Med. Assn.*, 1926, **87**, 2139) immunized goats with green-producing measles diplococci and their filtrates, and produced an antibacterial and antitoxic serum. From 4 to 6 cc. of immune goat serum was given to children one year old or older and to a few nurses, with a negative history of measles, after a definite exposure to measles. All persons who did not receive serum, and all who received serum five days or more after exposure, developed measles. Goat serum prevented measles in 45 per cent of persons who received serum on the fourth day after contact with measles patients, and in 97 per cent of those who received it within the first three days after exposure. All infants under one year of age who received serum after the fourth day after exposure developed measles. Ninety-eight per cent of infants given serum within

the first four days after exposure failed to show any signs of the disease. Reactions to the goat serum were observed in 12 per cent of those injected. Although the duration of passive immunity with immune goat serum, as with human convalescent measles serum, is only a few weeks, the serum appears to be useful in preventing measles in very young and sick children, and in stopping epidemics in institutions where the inconvenience of an epidemic is great and the mortality may be high.

An Epidemiologic Study of Endemic Typhus (Brill's Disease) in the Southeastern United States.—MAXCY (Public Health Reports, 1926, **41**, 2967–2990) refers to the work of others on endemic typhus, including the evidence for the identity of the disease with Mexican typhus, which corresponds to the *old-world* type of the disease. The endemic form is usually a disease of adults, chiefly of white males. The disease is predominantly one of summer and fall, in direct contrast with old-world typhus which occurs chiefly in winter and spring. Cases seem to show a grouping in respect of places of occupation, but not with respect to places of residence. Those engaged in "trade" especially those employed in food depots, groceries and feed stores and restaurants, furnish a suspiciously high incidence of cases. There is lacking the high incidence among the poor and uncleanly which marks the epidemic of European typhus. The mode of transmission is not established. It is rare that contact with a previous case can be shown—in other words, evidence of communication of the disease from one person to another is lacking. In general, the patients have been found free from either head lice or body lice. The seasonal distribution, the social condition of patients, and lack of communicability from person to person point against the louse as being implicated. It is suggested that a reservoir of infection may exist among rats and mice, and that it is from such a reservoir human infections occur.

PHYSIOLOGY

PROCEEDINGS OF

THE PHYSIOLOGICAL SOCIETY OF PHILADELPHIA

SESSION OF MAY 16, 1927

Available Carbohydrate in Food.—L. JONAS, and M. E. MORRISON (from the William Pepper Laboratory of Clinical Medicine, University of Pennsylvania). The object of this study has been to determine the effects of foods of various carbohydrate content on the blood sugar concentration of diabetic patients. In the first group that quantity of food was given which was intended to yield 25 gm. of carbohydrate.

On the first day a food containing approximately 10 per cent of carbohydrate was given, on the second day one of higher content, and on the third day usually one of high carbohydrate content, like bread. The blood was taken after a fast of at least twelve hours and then every half hour for two hours, and finally at the end of the third hour and analyzed by the method of Hagedorn and Jansen. Vegetables were prepared by adding just enough water to cover them and cooking for one and a half hours. In the interpretation of our results it was realized that the rate of absorption, the condition of the gastrointestinal tract, and the readiness with which the carbohydrate became available played an important part. In any particular patient it was hard to predict the result, but it would seem that in the severe cases, foods of high carbohydrate content and those in a liquid state, such as milk, caused a higher rise in the blood sugar curve than those of lower content. Foods of low-carbohydrate content were studied in a similar manner except that the amount of food given was that intended to yield 15 gm. of carbohydrate. For comparison, on the final day, a food of high-carbohydrate content was given. The table below gives the results for this series from quantities of food supposed to yield 15 gm. of carbohydrate.

Carbohydrate.	No. of cases.	Rise in blood sugar, mg. per 100 cc.				
		No rise.	0–20.	20–40.	40–60.	60–80.
Stringbeans	3	..	1	2		
Cabbage	6	..	4	1	1	
Bread	7	..	..	3	1	3
Oatmeal	2	..	2			
Spinach	8	6	1	1		

It is evident that vegetables of low-carbohydrate content caused very little or no rise in the blood sugar concentration in most of the cases tested so that when such foods are given less insulin is required than when foods containing a higher carbohydrate content are used.

Optical Isomers of Cystine.—J. C. Andrews and E. J. De Beer (from the Department of Physiological Chemistry, School of Medicine, University of Pennsylvania). These experiments record attempts to determine the relation between some of the physical properties of the optical isomers of cystin. Further knowledge of the stereochemistry of this compound is desirable in order that the physiologically important isomers may be more clearly defined and their exact properties studied. The methods used here consist in preparing very pure samples of cystin of various optical activities from -204 to $+12$ and in determining the isoelectric solubilities of these different forms at 25° C. The optical activity of the isoelectric solutions was also measured. An optically active compound, such as cystin, may exist in the following forms: Levorotatory (l), dextrorotatory (d), internally compensated or meso (m), and racemic compound (dl). Each of these phases has its own solubility and will produce, at a given temperature, a constant concentration of cystin in the solution, provided a solid sample of sufficient size is used to permit saturation with *all* phases present. At the same time the optical activity of the water solution will be the result of the relative solubilities of the two active phases concerned (d and l). Absence of mixed crystals is, thus far, assumed.

Solubilities were determined on the isoelectric solutions by the Folin-Looney method which was checked against micro-Kjeldahl determinations. Optical activity figures were read in an accurate Schmidt and Haensch polariscope with a 4-dm. tube. These readings were accurate to within $\pm 0.01°$.

The results of the solubility measurements permit calculation of the probable solubilities of the various isomers. These figures, however, are not final, since much further work remains to be done and certain discrepancies in the figures for optical activity remain to be explained. The following figures, expressed in grams cystin per liter at $25° \pm 0.1°$ C. are at present accepted by the authors. l-cystin, 0.08 g.; d-cystin, 0.32 g.; m-cystin, 0.083 g.; dl-cystin, 0.152 g. The relative solubilities determined for the d- and l-forms are in contradication to the usual view that optical antipodes have identical solubilities but they support earlier figures by Moerner (*Zeit. f. Physiol. Chem.*, 1899, **28**, 595) who found his preparations of d-cystin to be over three times as soluble as the l-form.

A New Method for the Isolation of Certain Extractives of Muscle. Study of their Composition.—Wilson D. Langley (from the Department of Physiological Chemistry, University of Pennsylvania Medical School). The nature of the chemical reactions which occur in muscle are as yet not clearly understood. The compounds which have thus far been isolated from muscle have afforded but little insight into the possible reactions in which they may take part. It is probable that more complete knowledge concerning the chemical composition of the substances which have not yet been identified will lead to an understanding of some of the chemical reactions which go on in muscle. With this in view, an attempt is being made to isolate and to identify certain extractives of muscle.

The isolation of an imidazole compound of unknown structure having the composition $C_{14}H_{18}N_4O_7.H_3PO_4$ was reported by the writer in 1925 (*Proc. Soc. Exper. Biol. and Med.*, 1925, **22**, 234). Since that time a method by which the new compound is obtained sufficiently pure for further study has been developed. The method yields in addition several preparations which are thought to be composed chiefly of single compounds. These preparations have been obtained according to the outline given below, and are being studied to determine the structures of the compounds present.

Muscle is extracted with water and the solution obtained is evaporated *in vacuo* until creatin separates. The creatin and some salts are removed by filtration. Alcohol is added to the filtrate until the resulting solution is 70 per cent alcohol. The remaining solution is neutralized to Congo Red by use of HCl, and the resulting hydrochlorids are divided according to their solubilities in ether, butyl alcohol, absolute ethyl alcohol, and methyl alcohol. Each fraction is in turn freed of Cl, SO_4 and PO_4, and converted to copper salts by use of CuO. The copper salts are then purified further by use of the same solvents. Aside from lactic acid, 7 final fractions have been obtained thus far. These fractions may be designated as follows: (1) Soluble in butyl alcohol-ether mixture (1:1); (2) soluble in butyl alcohol; (3) soluble in absolute ethyl alcohol; (4) soluble in 70 per cent methyl alcohol—the

salt of the imidazole compound reported previously; (5) soluble in 50 per cent methyl alcohol; (6) soluble in water; (7) insoluble in water.

In order to compare the imidazole compound (4) with carnosin, each has been titrated by use of indicators over the pH range 2 to 12.6. Carnosin has a second acidic group which functions from about pH 10.8 to above 12.6. This group is probably the =NH group in the imidazole ring, and its acidic nature probably accounts for the formation of the dimetallic salts of histidin and of carnosin. Since the possibility of enolization in the imidazole ring is excluded, and since the =NH group is acidic, it is probable that similar groups in purines and pyrimidins may function as acids without the occurrence of enol forms. The compound (4) lacks the strong basic group that is present in carnosin, and has instead a weakly basic group. Otherwise, the acidic and basic groups present in (4) are similar to those present in carnosin.

Studies upon the extractives of muscle are being continued.

On the Mechanism of the Production of Electromotive Forces in Living Tissues.—W. R. Amberson and H. Klein (from the Department of Physiology, University of Pennsylvania Medical School). The influence of pH upon the electromotive phenomena of the frog's skin and upon the injury E. M. F. of the frog's gastrocnemius has been studied. When the pH is gradually lowered the normal skin potential, that is, that E. M. F. observed across the skin when in contact with the same salt solution on both sides, disappears at about pH = 3.8. The "concentration effect" across the skin, that is, the E. M. F. arising when it separates two solutions of different salt concentration, is reduced to zero at about the same pH. At lower pH values the concentration E. M. F. is reversed. Thus above pH = 3.8 the more dilute solution is electropositive; below this value it becomes electronegative. If now the pH is gradually raised a new reversal point at about pH =4.7 is found. Above this point the concentration effect again has such a polarity that the more dilute solution is electropositive. The skin potential does not reappear. The concentration E. M. F. may now be reversed repeatedly by adjusting the pH, the isoelectric point remaining constant at about pH =4.7. These observations are believed to support the hypothesis that the electromotive phenomena in this material are determined by the electrical charge of the membrane. Above its isoelectric point the membrane is negatively charged and behaves as if it permitted positively charged cations to pass, but prevented or retarded the movement of negatively charged anions. The resulting ionic orientation produces the E. M. F. across the membrane. Below the isoelectric point the membrane is positively charged and behaves as if it permitted negatively charged anions to pass but prevented or retarded the movement of positively charged cations. It is suggested that electrostatic forces between the charged surfaces and the ions involved may determine this behavior.

The injury E. M. F. of muscle may be similarly reversed by low pH, the reversal point being about pH 3.7. When a muscle is brought into contact with an unbuffered Ringer solution acidified with HCl, and its injury E. M. F. measured from time to time, it is found that the rate at which the E. M. F. changes is profoundly influenced by the pH.

Below pH 3.7 the injury E. M. F. reduces to zero and then reverses, the injured region becoming electropositive. Such reversals never occur above this value. Ultimately, on either side of the isoelectric point, the injury E. M. F. reaches a constant value, apparently representing an equilibrium condition, which may persist for hours. These constant values are believed to represent the magnitude of the injury E. M. F. at the pH of the experiment. When these equilibrium values are plotted against the pH, a curve altogether similar to those constructed for the frog-skin-concentration effects is obtained. This gives evidence that the injury E. M. F. of muscle is due to a concentration effect within the tissue whose polarity may be reversed when, by an increase in H-ion concentration, the charge upon the membranes involved is reversed.

A New Method for the Microscopic Study of Living Growing Tissues by the Introduction of a Transparent Chamber in the Rabbit's Ear.—J. C. SANDISON (from the Laboratory of Anatomy, School of Medicine, University of Pennsylvania). Transparent living tissues, thin enough to transmit sufficient light for microscopic observation, have been widely used for many years in the study of cell growth and behavior. The classical object has been the transparent tail of the amphibian larva, from which has been gained much of our present knowledge of the growth and reactions of bloodvessels, lymphatics, nerves, connective-tissue cells, and wandering cells. While many facts of fundamental importance have been discovered, still the question frequently arises whether there may not be differences in the growth and behavior of mammalian, as compared with amphibian cells and tissues.

The only translucent regions in mammals adaptable for microscopic study are the omentum and mesentery. These have been used, but their availability is greatly limited, owing to the necessity of anesthetizing the animal and to the inflammation which is produced by the unusual exposure. The few hours' period, during which such studies may be continued, is too short to permit observations on growth processes.

In the "tissue-culture" method, invented by R. G. Harrison (1902), and employed by others, the tissues are entirely removed from the body, and the growth changes which take place diverge greatly from the normal.

The desire to obtain a region in which the growth and behavior of living mammalian tissues could be satisfactorily studied microscopically led to an attempt to devise a new method. The suggestion came from the classical glass-chamber method of E. Ziegler (1875), which as employed by him and others, particularly A. Maximow (1902), consists of the construction of a chamber, made from two cover-glasses fastened together with a very thin space between them. This chamber was placed under the skin and left for varying lengths of time, and after its removal tissues which had grown into it were stained and studied; Maximow succeeded in watching the living cells in the chamber after its removal, but only for an hour and a half.

Until recently there had been no mammalian object available for making, over a long period of time, continuous microscopic observations of a tissue thin enough to differentiate clearly the individual cells which constitute it; nor had there been any method by which, in the living

mammal, new-forming tissue could be watched for months while it grew into a region which was free from any previously-formed tissue and yet contained a normal body fluid. Such an object was developed in the mammal three years ago by the author (J. C. Sandison, *Anat. Record*, 1924) by means of a transparent chamber placed in a hole cut from the rabbit's ear. By this method, which has since been perfected, a very thin layer (15 to 20 μ) of the animal's new forming tissue grows into the chamber space and one can study, besides normal circulatory phenomenon, the individual cells of the tissue, their origin and fate; the growth of endothelium; smooth muscle; nerves; and so forth, in a manner similar to that which has been used in the tadpole mainly by E. R. and E. L. Clark—namely, the following of the same cells day after day, over a period of months with the oil-immersion lens. Moreover, this layer of tissue remains a thin one even after it reaches the adult stage, and one may continue to study the cells and to perform experiments for as long as three and a half months.

The possibilities of the method are numerous. A field is furnished for carrying out studies somewhat similar to those of tissue cultures. Also, the opportunity is afforded to study the part which the various cells play in the formation of new tissue, in phagocytosis, and in other reactions connected with function and growth, in determining the mode of growth of blood capillaries, lymphatics, nerves, smooth muscle, connective tissue, and so forth, in a mammal. Studies on a very few of these problems have already been made; and are to be published in the near future, the field is large, however, and concentrated studies must be continued.

Correction.—On page 572 of the April number, line 22, abstracting Medearis and Minot's article, the words "spontaneous remission" should be changed to read "remission following the special diet treatment."

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